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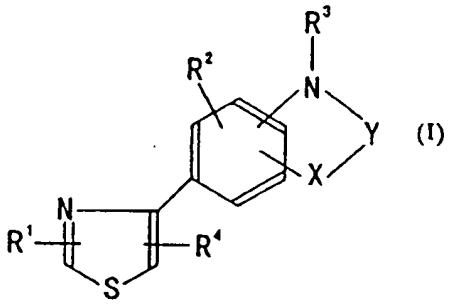

(I)

(57) Abstract

Thiazole derivatives of formula (I) wherein R^1 is amino; lower alkylamino; heterocyclic ring containing nitrogen which may be substituted with halogen(s), amino(s), N-oxide, lower alkoxy(s), lower alkyl(s), lower alkoxycarbonyl(s), halo(lower)-alkoxycarbonyl(s), cyano(s), cyclo(lower)alkylamino(s), lower alkylamino(s), heterocyclic ring containing nitrogen (s), or oxo; or lower alkyl substituted with heterocyclic ring containing nitrogen; R^2 is hydrogen; hydroxy; lower alkyl; or lower alkoxy; R^3 is hydrogen; lower alkyl which may be substituted with acyl(s), N-mono(or di)(lower)alkylamino(s), lower alkylthio(s), lower alkoxy(s), carboxy(s), heterocyclic ring containing nitrogen(s), lower alkynyl(s), halogen(s), or aryl(s); acyl; or cyclo(lower)alkyl; R^2 and R^3 may be linked together to form lower alkylene, R^4 is hydrogen; lower alkyl; halogen; or lower alkylthio; X is lower alkylene which may be substituted with heterocyclic ring containing nitrogen(s), halogen(s), hydroxy(s), phenyl(lower)alkylidene(s), N-mono(or di)-(lower)alkylamino(lower)alkylidene(s), hydroxy(lower)alkylidene(s), or lower alkoxyimino(s); cyclo(lower)alkylidene; carbonyl; or thio; Y is lower alkylene which may be substituted with oxo, or thioxo; and X and Y may be linked together to form lower alkenylene, X and N are respectively bonded to the adjoining carbon atoms on the benzene ring, or a pharmaceutically acceptable salt thereof, which are useful as a medicament.

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DESCRIPTION

THIAZOLE DERIVATIVES

TECHNICAL FIELD

This invention relates to new thiazole derivatives or a pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some thiazole derivatives have been known as described, for example, in Japanese Patent Publication (Kokoku) No. 46-15935.

DISCLOSURE OF INVENTION

This invention relates to new thiazole derivatives. More particularly, this invention relates to new thiazole derivatives and a pharmaceutically acceptable salt thereof which have pharmacological activities, processes for preparation thereof, a pharmaceutical composition comprising the same and a use of the same.

Accordingly, one object of this invention is to provide the useful thiazole derivatives and a pharmaceutically acceptable salt thereof which possess an anti-inflammatory activity, an immunomodulating activity, an inhibitory activity on the production of gamma interferon (IFN-γ) and an inhibitory activity on the production of tumor necrosis factor (TNF).

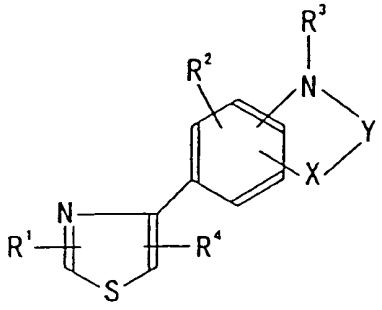
Another object of this invention is to provide processes for preparation of the thiazole derivatives and a salt thereof.

A further object of this invention is to provide a pharmaceutical composition comprising said thiazole derivatives or a pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a use of said

thiazole derivatives or a pharmaceutically acceptable salt thereof as a medicament for prophylactic and/or therapeutic treatment of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, IFN-γ mediated diseases, TNF mediated diseases and the like in human being and animals.

The object thiazole derivatives of the present invention can be represented by the following formula (I):



(I)

wherein

R^1 is amino;

lower alkylamino;

heterocyclic ring containing nitrogen which may be substituted with

halogen(s), amino(s), N-oxide, lower alkoxy(s), lower alkyl(s), lower alkoxycarbonyl(s), halo(lower)-alkoxycarbonyl(s), cyano(s), cyclo(lower)alkylamino(s), lower alkylamino(s), heterocyclic ring containing nitrogen(s), or oxo; or

lower alkyl substituted with heterocyclic ring containing nitrogen;

R^2 is hydrogen;

hydroxy;

lower alkyl; or

lower alkoxy;

R^3 is hydrogen;

lower alkyl which may be substituted with

acyl(s), N-mono(or di)(lower)alkylamino(s), lower alkylthio(s), lower alkoxy(s), carboxy(s), heterocyclic ring containing nitrogen(s), lower alkynyl(s), halogen(s), or aryl(s);

acyl; or

cyclo(lower)alkyl;

R^2 and R^3may be linked together to form lower alkylene,

R^4 is hydrogen;

lower alkyl;

halogen; or

lower alkylthio;

X is lower alkylene which may be substituted with

heterocyclic ring containing nitrogen(s), halogen(s), hydroxy(s), phenyl(lower)alkylidene(s), N-mono(or di)-(lower)alkylamino(lower)alkylidene(s), hydroxy(lower)alkylidene(s), or lower alkoxyimino(s);

cyclo(lower)alkylidene;

carbonyl; or

thio;

Y is lower alkylene which may be substituted with

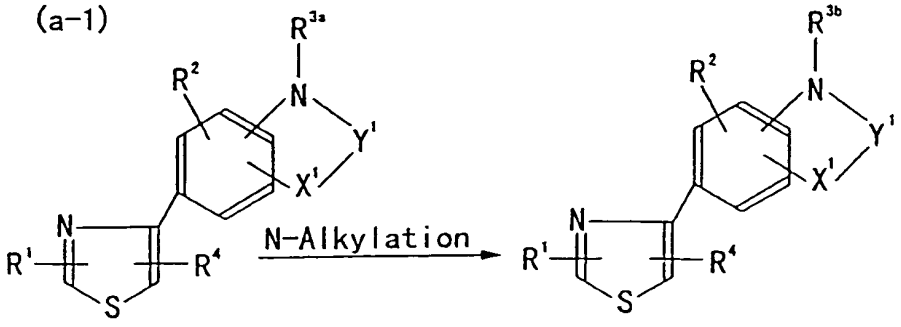
oxo, or thioxo; and

X and Y may be linked together to form lower alkenylene,

X and N are respectively bonded to the adjoining carbon atoms on the benzene ring,

or a pharmaceutically acceptable salt thereof.

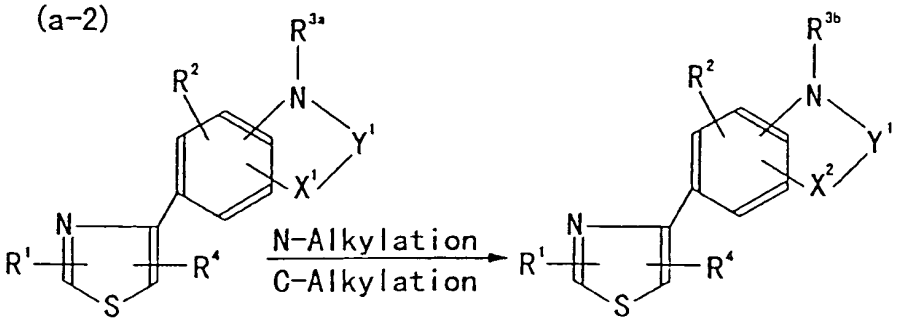
(a-1)



(Ic)'
or a salt thereof

(Id)'
or a salt thereof

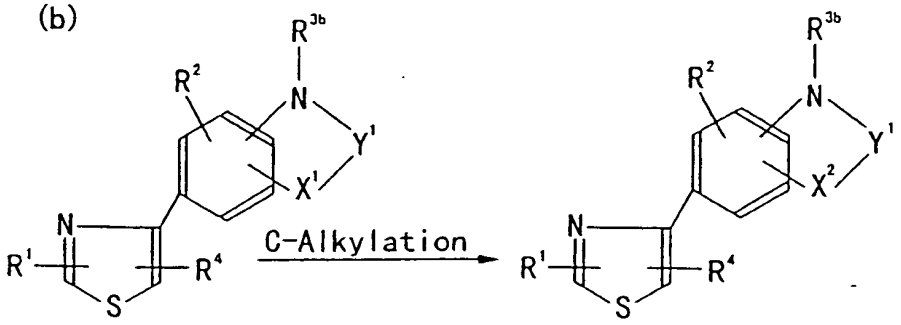
(a-2)



(Ic)'
or a salt thereof

(Id)''
or a salt thereof

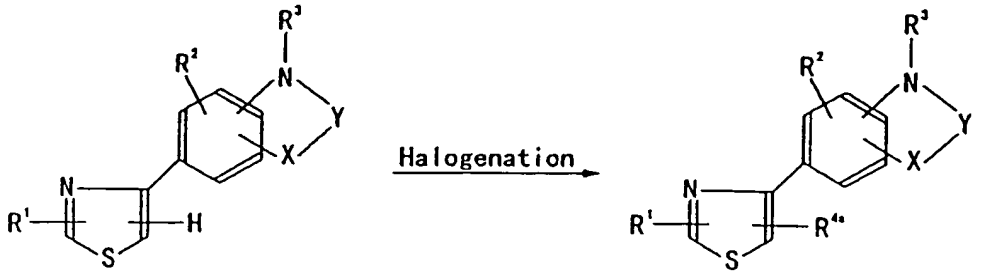
(b)



(Ic)''
or a salt thereof

(Id)''
or a salt thereof

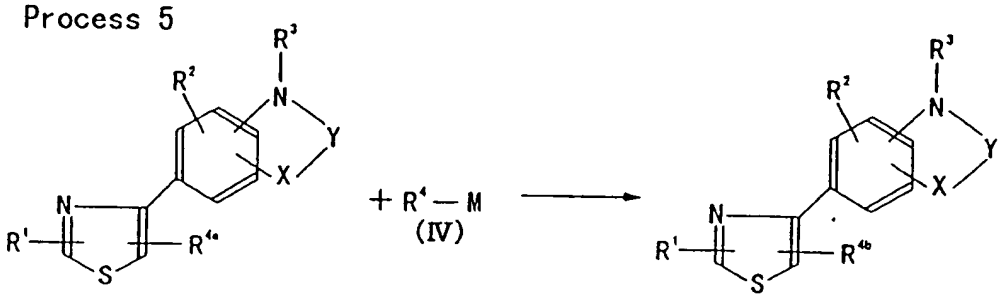
Process 4



(Ie)
or a salt thereof

(If)
or a salt thereof

Process 5



(If)
or a salt thereof

(Ig)
or a salt thereof

wherein R^1, R^2, R^3, R^4, X and Y are each as defined above,

R^{3a} is hydrogen,

R^{3b} is lower alkyl,

R^{4a} is halogen,

R^{4b} is lower alkylthio,

M is alkaline metal,

X^1 is lower alkylene,

X^2 is cyclo(lower)alkylene,

X^3 is lower alkylene which may have alkyl or cycloalkyl,

Y^1 is carbonyl,

Y^2 is methylene, and

Z is acid residue.

BEST MODE FOR CARRYING OUT THE INVENTION

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include a metal salts such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylene diamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), a salt with alkyl halide [e.g., alkyl fluoride (methyl fluoride, ethyl fluoride, etc.), alkyl chloride (methyl chloride, ethyl chloride, etc.,), alkyl bromide (methyl bromide, ethyl bromide, etc.), alkyl iodide (methyl iodide, ethyl iodide, etc.,)], and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 7 carbon atom(s), unless otherwise indicated, preferably 1 to 6 carbon atom(s), more preferably 1 to 4 carbon atom(s).

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "lower alkylamino", "cyclo(lower)alkylamino", "cyclo(lower)alkyl", "lower alkylthio", "N-mono(or di)(lower)alkylcarbamoyl", "N-mono(or di) (lower)alkylamino", "N-mono(or di) (lower)alkylamino(lower)-alkylidene", and "lower(alkyl)sulfonyl" may include straight or branch one such as methyl, ethyl, propyl, 1-ethylpropyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl,

pentyl, neopentyl, t-pentyl, hexyl, heptyl and the like.

Suitable "heterocyclic ring containing nitrogen" and "heterocyclic moiety" in the term "heterocyclic carbonyl" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one nitrogen atom. And especially preferable heterocyclic ring containing nitrogen may be ones such as

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, tetrahydropyridyl (e.g., 1,2,3,6-tetrahydropyridyl, 1,4,5,6-tetrahydropyridyl, etc.), pyrimidinyl, pyrazinyl, dihydropyridazinyl, tetrahydropyridazinyl, triazolyl (e.g., 1H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc., ;

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, azacycloheptyl, azacyclooctyl, etc., ;

unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, isoindolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl,indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl,etc.,), dihydrotriazolopyridazinyl, triazolopyridyl (e.g., [1,2,4]triazolo[4,3-a]pyridyl, etc.), imidazopyrazinyl(e.g., imidazo[1,2-a]pyrazinyl, etc.), etc.,;

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, dihydroisoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 2,5-oxadiazolyl, etc.,), etc., ;

saturated 3 to 8-membered heteromonocyclic group containing 1

to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, etc., ;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc., ;

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl), etc.,;

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.,;

unsaturated condensed heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc., and the like.

Suitable "acyl" may include aliphatic acyl group and acyl group containing an aromatic or heterocyclic ring.

And, suitable examples of the said acyl may be lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.); aroyl (e.g. benzoyl, naphthoyl, etc.); lower alkoxyaroyl (e.g. methoxyphenylcarbonyl, ethoxyphenylcarbonyl, propoxy-phenylcarbonyl, isopropoxyphenylcabonyl, methoxynaphthylcarbonyl, ethoxynaphthylcarbonyl, propoxynaphtylcarbonyl, isopropoxynaphthyl-carbonyl, etc.); lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxy-carbonyl, propoxycarbonyl, 1-cyclopropylethoxycarbonyl, isopropoxy-carbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.); ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, etc.); ar(lower)alkoxycarbonyl (e.g. benzyloxy-carbonyl, phenethyloxycarbonyl, etc.); heterocyclic carbonyl

("heterocyclic moiety" in the term "heterocyclic carbonyl" can be referred above); bridged cyclic(lower)alkanecarbonyl (e.g. bicyclo-[2.2.1]hept-2-yl-carbonyl, bicyclo[3.2.1]oct-2-yl-carbonyl, bicyclo-[3.2.2]non-2-yl-carbonyl, bicyclo[3.2.2]non-3-yl-carbonyl, bicyclo-[4.3.2]undec-2-yl-carbonyl, bicyclo[4.3.2]undec-3-yl-carbonyl, bicyclo-[2.2.2]oct-2-en-2-yl-carbonyl, bicyclo[3.2.2]non-3-en-3-yl-carbonyl, tricyclo[5.3.1.1]dodec-2-yl-carbonyl, tricyclo[5.3.1.1]dodec-3-yl-carbonyl, adamantylcarbonyl, etc.); cyclo(lower)alkanecarbonyl (e.g. cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, etc.), carbamoyl which may be substituted with mono- or di-(lower)alkyl (e.g. dimethylcarbamoyl, etc.), sulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.) and the like.

Suitable "lower alkoxy" and "lower alkoxy moiety" in the terms "lower alkoxyaroyl", "lower alkoxycarbonyl", "halo(lower)alkoxycarbonyl", and "lower alkoxyimino" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy, heptyloxy and the like.

Suitable "lower alkylene" may include straight or branched one having 1 to 7 carbon atom(s), such as methylene, ethylene, dimethylethylene, trimethylene, 1-methyltrimethylene, 1,1-dimethyltrimethylene, 2,2-dimethyltrimethylene, 1-ethyltrimethylene, (1,1-dipropyl)trimethylene, (1,1-diethyl)trimethylene, tetramethylene, pentamethylene, hexamehylene, or the like, preferably one having 1 to 6 carbon atom(s), more preferably one having 1 to 4 carbon atom(s).

Suitable "halogen" and "halogen moiety" in the terms "mono(or di or tri)halo(lower)alkyl" and "halo(lower)alkoxycarbonyl" may include chlorine, bromine, fluorine and iodine.

Suitable "alkaline metal" may include lithium, sodium, potassium, and the like.

Suitable "cyclo(lower)alkylidene" may include cyclopropylidene,

cyclobutylidene, cyclopentylidene, cyclohexylidene, cycloheptylidene, and the like.

Suitable "lower alkynyl" may include ethynyl, propynyl, propenyl, butynyl, pentynyl, hexynyl, heptynyl, and the like.

Suitable "aryl" may include phenyl, lower alkylphenyl (e.g. tolyl, ethylphenyl, propylphenyl, etc.), naphthyl, or the like.

Suitable "lower alkylidene moiety" in the terms "phenyl(lower)-alkylidene", "cyclo(lower)alkylidene", "N-mono(or di) (lower)-alkylamino(lower)alkylidene", and "hydroxy(lower)alkylidene" may include methylidene, ethylidene, propylidene, butylidene, pentylidene, hexylidene, heptylidene, or the like.

Suitable "cyclo(lower)alkyl" and "cyclo(lower)alkyl moiety" in the term "cyclo(lower)alkylamino" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

Suitable "lower alkenylene" may include straight or branched one having 2 to 7 carbon atom(s), such as vinylene, propenylene, 1-pentenylene, 2-pentenylene, 1-butenylene, 2-butenylene, 1-hexenylene, 2-hexenylene, 3-hexenylene, 1-heptenylene, 2-heptenylene, 3-heptenylene, or the like.

The preferred embodiments of the object compound (I) are as follows:

wherein

R^1 is amino;

lower alkylamino;

heterocyclic ring containing nitrogen which may be substituted with

halogen(s), amino(s), N-oxide, lower alkoxy(s), lower alkyl(s), lower alkoxycarbonyl(s), halo(lower)-alkoxycarbonyl(s), cyano(s), cyclo(lower)alkylamino(s),

lower alkylamino(s), heterocyclic ring containing nitrogen(s), or oxo; or

lower alkyl substituted with heterocyclic ring containing nitrogen;

R^2 is hydrogen;

hydroxy;

lower alkyl; or

lower alkoxy;

R^3 is hydrogen;

lower alkyl which may be substituted with

lower alkanoyl(s), cyclo(lower)alkanecarbonyl(s), bridged cyclic(lower)alkylcarbonyl(s), aroyl(s), lower alkoxyaroyl(s), heterocyclic carbonyl(s), lower alkoxycarbonyl(s), carbamoyl(s), N-mono(or di)(lower)-alkylcarbamoyl(s), N-mono(or di)(lower)alkylamino(s), lower alkylthio(s), lower alkoxy(s), carboxy(s), heterocyclic ring containing nitrogen(s), lower alkynyl(s), halogen(s), or aryl(s);

lower alkanoyl(s) or lower(alkyl)sulfonyl(s); or

cyclo(lower)alkyl;

R^2 and R^3 may be linked together to form lower alkylene,

R^4 is hydrogen;

lower alkyl;

halogen; or

lower alkylthio;

X is lower alkylene which may be substituted with

heterocyclic ring containing nitrogen(s), halogen(s), hydroxy(s), phenyl(lower)alkylidene(s), N-mono(or di)-(lower)alkylamino(lower)alkylidene(s), hydroxy(lower)alkylidene(s), or lower alkoxyimino(s);

cyclo(lower)alkylidene;

carbonyl; or

thio;

Y is lower alkylene which may be substituted with

oxo, or thioxo; and

X and Y may be linked together to form lower alkenylene,

X and N are respectively bonded to the adjoining carbon atoms on the benzene ring,

or a pharmaceutically acceptable salt thereof.

The more preferred embodiments of the object compound(I) are as follows:

wherein

R^1 is amino;

methylamino; or

pyridyl, [1,2,4]triazolo[4,3-a]pyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, imidazo[1,2-a]pyrazin-2-yl, 4-pyrimidinyl, 2-chloro-4-pyridyl, 2-chloro-5-pyridyl, 2-amino-5-pyridyl, pyridine-1-oxide-4-yl, pyridine-1-oxide-3-yl, 2-methoxypyridin-4-yl, 1-methyl-1,2,3,6-tetrahydropyridin-4-yl, 1-methyl-2-oxopyridin-4-yl, 2-methylpyridin-5-yl, 3-methylpyridin-4-yl, 2-ethoxycarbonylpyridin-4-yl, 1-(1-chloroethoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl, 2-cyanopyridin-4-yl, 2-(2-cyclopropylamino)pyridin-4-yl, 2-(1-imidazolyl)pyridin-4-yl, or 2-oxopyridin-4-yl;

(pyridin-3-yl)methyl;

R^2 is hydrogen;

hydroxy;

methyl; or

methoxy;

R^3 is hydrogen;

methyl, ethyl, propyl, 1-ethylpropyl, isopropyl, butyl, sec-butyl, pentyl, neopentyl, hexyl, propionylmethyl, pivaloylmethyl, adamantylcarbonylmethyl, benzoyl, m-methoxybenzoylmethyl, isonicotinoylmethyl, ethoxycarbonylmethyl, 2-(N,N-dimethylamino)ethyl, 2-methylthioethyl, 2-methoxyethyl, carboxymethyl, (N,N-dimethylcarbamoyl)methyl, (pyridin-4-yl)-methyl, (pyridin-3-yl)methyl, (pyridin-2-yl)methyl, carbamoylmethyl, 2-propynyl, 2,2-difluoroethyl, or benzyl;

acetyl or methylsulfonyl; or

cyclopentyl, cyclohexyl, or cycloheptyl;

R^2 and R^3 may be linked together to form ethylene,

R^4 is hydrogen;

methyl;

chloro;

bromo; or

methylthio;

X is methylene, ethylene, 1-methyltrimethylene, 1,1-dimethyltrimethylene, 2,2-dimethyltrimethylene, trimethylene, tetramethylene, (1-ethyl)trimethylene, (1,1-dipropyl)-trimethylene, (1,1-diethyl)trimethylene, 1-(1-imidazolyl)-trimethylene, fluoromethylene, difluoromethylene, hydroxymethylene, styrylidene, 2-(N,N-dimethylamino)-ethylidene, hydroxyethylidene, or methoxyiminomethylene;

cyclopropylidene, cyclobutylidene, cyclopentylidene, or cyclohexylidene;

carbonyl; or

thio;

Y is methylene, 1-oxoethylene, 1-oxotrimethylene, carbonyl, or

thiocarbonyl; and

X and Y may be linked together to form vinylene,

X and N are respectively bonded to the adjoining carbon atoms on the benzene ring,

or a pharmaceutically acceptable salt thereof.

The furthermore preferred embodiments of the object compound(I) are as follows:

wherein

R^1 is heterocyclic ring containing nitrogen,

R^2 is hydrogen or lower alkyl,

R^3 is lower alkyl,

R^4 is hydrogen,

X is lower alkylene, and

Y is carbonyl,

or a pharmaceutically acceptable salt thereof.

The still further preferred embodiments of the object compound(I) are as follows:

wherein

R^1 is pyridyl, and

R^2, R^3, R^4, X and Y are each as defined above,

or a pharmaceutically acceptable salt thereof.

The most preferred embodiments of the object compound(I) are 1-isoproyl-8-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one or 1-isoproyl-5,5-dimethyl-7-[2-(4-

pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one.

The main processes for preparing the object compound (I) and the starting compounds of the present invention are explained in detail in the following.

Process 1:

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) or a salt thereof.

Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as N,N-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (II) with phosphorus trichloride or phosgene and the like.

Suitable salts of the compounds (II) and (III) can be referred to the ones as exemplified for the compound (I).

Suitable acid residue may include inorganic acid residue (e.g., halogen such as chlorine, bromine, fluorine or iodine); organic acid residue (e.g., acyloxy such as acetoxy; sulfonyloxy such as benzenesulfonyloxy, tosyloxy, methanesulfonyloxy).

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely affect the reaction. These conventional solvents may also be

used in a mixture of two or three of them.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)aklylmorphorine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

The compound (III) or a salt thereof can be prepared in accordance with the method disclosed in the Preparations described later or similar manners thereto.

The reaction can be referred to that of Examples 1~7, 32~34, 37, 39, 41, 44, 46, 50, 53, 59, 60, 78, 94~97, 99, 104, 107, 109, 111, 113, 115, 117, 129.

Process 2

The compound (Ib) or a salt thereof can be prepared by reducing the compound (Ia) or a salt thereof.

Suitable salts of the compounds (Ia) and (Ib) can be referred to the ones as exemplified for the compound (I).

This reaction can be referred to that of Examples 1-(1), 2-(1), 8-(2), 36, 38, 40, 42, 45, 63, 80, 131.

Process 3

The compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to

(a-1) N-alkylation reaction of the imino group wherein R^3 is hydrogen,

(a-2) N-alkylation reaction of the imino group and C-alkylation reaction of the adjacent carbon atom to carbonyl group wherein X is methylene and R^3 is hydrogen,

(b) C-alkylation reaction of the adjacent carbon atom to

carbonyl group wherein X is methylene and R^3 is lower alkyl.

Suitable salts of the compounds (Ic) and (Id) can be referred to the ones as exemplified for the compound (I).

This reaction can be referred to that of Examples 6-(1), 6-(2), 8-(1), 9~22, 23-(1), 24-(1), 25-(1), 26-(1), 27-(1), 28-(1), 29-(1), 30-(1), 31-(1), 48, 72~77, 79, 81, 83~88, 91, 98, 100, 105, 108, 110, 112, 114, 116, 118~124, 127, 128, 130, 132 [(a-1)], Example 3-(1) [(a-2)], Example 5-(1), 61, 62 [(b)].

In order to show the utilities of the thiazole derivatives (I) and a pharmaceutically acceptable salt thereof of the present invention, pharmacological test data of the representative compound of the thiazole derivatives (I) are illustrated in the following.

Process 4

The compound (If) or a salt thereof can be prepared by halogenating the compound (Ie) or a salt thereof.

Suitable salts of the compounds (If) and (Ie) can be referred to the ones as exemplified for the compound (I).

This reaction can be referred to that of Examples 6-(1)-(1), 6-(1)-(2).

Process 5

The compound (Ig) or a salt thereof can be prepared by reacting the compound (If) or a salt thereof with the compound (Ig) or a salt thereof.

Suitable salts of the compounds (Ig) can be referred to the ones as exemplified for the compound (I).

This reaction can be referred to that of Examples 6-(1)-(1)-(1).

The above processes 1 to 5 are main ones for the purpose of preparing the present thiazole derivatives(I), therefore, there is not limited to them in the present invention.

Otherwise, the following processes of Examples can be referred to those of Example 35; 43(including Examples 51, 89, 106, 126, and 133); 47; 49; 52; 54(including Example 101); 55-58; 64-71; 82(including Example 125); 90; 92; 93; 102(including Example 103).

Effect on Con A-induced hepatitis in mice

[I] Test Method :

(1) Mice

Female BALB/c mice were purchased from the Shizuoka Experimental Animal Center (Shizuoka, Japan), and were used at 7-10 week of age.

(2) Treatment of mice

Con A (Vector Laboratories, Inc.) was dissolved in pyrogen-free saline and administered to mice via the tail vein at a dose of 0.3 mg/mouse. Drugs suspended in 0.1% methylcellulose were administered to mice orally (p.o.) 1 hour before Con A injection.

(3) Assay for plasma transaminase activities

Plasma from individual mice was obtained 24hr after Con A injection. Plasma transaminase activity was measured by the standard photometric method using a bichromatic analyzer (model 100; Abbott Laboratories).

[II] Test Compound:

(a) 6-[2-(4-pyridyl)thiazol-4-yl]-3,4-dihydro-1-methyl-2(1H)-quinolinone [Example 2]

(b) 6-[2-(4-pyridyl)thiazol-4-yl]-1-methyl-1,2,3,4-tetrahydroquinoline [Example 2-(1)]

(c) 5-[2-(4-pyridyl)thiazol-4-yl]oxindole [Example 3]

(d) 5-[2-(4-pyridyl)thiazol-4-yl]-1,3,3-trimethyloxindole [Example 3-(1)]

(e) 1'-methyl-5'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole] [Example 4]

(f) 1'-isopropyl-5'-[2-(4-pyridyl)thiazol-4-yl]spiro-[cyclopropane-1,3'-oxindole] [Example 5-(1)]

(g) 1-isopropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one [Example 6-(1)]

(h) 1-isobutyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one [Example 6-(2)]

(i) 4-{4-(1'-methylspiro[cyclopropane-1,3'-oxindol-5'-yl])thiazol-2-yl}pyridine 1-oxide [Example 51]

(j) 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]oxindole [Example 60]

(k) 1'-methyl-5'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclobutane-1,3'-oxindole] [Example 62]

(l) 1-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one [Example 72]

(m) 1-ethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one [Example 73]

(n) 1-butyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride [Example 75]

(o) 1-(2,2-difluoroethyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride [Example 76]

(p) 1-(s-butyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one [Example 83]

(q) 1-cyclohexyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride [Example 87]

(r) 4-[4-(1-isopropyl-1,3,4,5-tetrahydro-2-oxo-2H-1-benzazepin-7-yl)-thiazol-2-yl]pyridine 1-oxide [Example 89]

(s) 1-isopropyl-5,5-diethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one [Example 108]

(t) 5,5-dipropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one [Example 109]

[III] Test Result:

Drug Example No.	Dose (mg/kg)	Inhibition(%)
2	32	90.1
2-(1)	32	86.9
3	32	88.7
3-(1)	32	91.6
4	32	88.9
5-(1)	32	87.0
6-(1)	32	96.9
6-(2)	32	85.6
51	32	93.6
60	32	87.2
62	32	87.4
72	32	91.3
73	32	91.4
75	32	85.7
76	32	82.2
83	32	96.6
87	32	96.3
89	32	98.2
108	32	96.3
109	32	94.7

Effect on in vitro cytokine production

[I] Test method

Spleens from BALB/c mice were removed, and single cell suspensions were prepared in culture medium (RPMI 1640 containing 2

mmol/l L-glutamine, 50 units/ml penicillin, and 50 μg/ml streptomycin, 5 $\times 10^{-5}$ mol/l 2-mercaptoethanol and 10% fatal calf serum). The cells were seeded into 24-well culture plates at a concentration of 2×10^6 cells per well in a volume of 1 ml culture medium and stimulated with 2 μg/ml of concanavalin A. Drugs dissolved in dimethylsulfoxide (DMSO) were diluted in culture medium and added at the initiation of culture. After 24 hr incubation in a humidified incubator (37°C, 5 % CO_2), culture supernatants were obtained. TNF and IFN-γ concentrations in the supernatants were determined by enzyme-linked immunosorbent assay (ELISA).

[II] Test compound

1-isopropyl -7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one [Example 6-(1)]

[III] Test result

Drug	Dose (μg/ml)	Inhibition (%)	
		TNF	IFN-γ
Example 6-(1)	1	11.9	61.8
Example 6-(1)	10	80.5	100

The thiazole derivatives (I) and a pharmaceutically acceptable salt thereof of the present invention possess an anti-inflammatory activity, an immunomodulating activity, an inhibitory activity on the production of gamma interferon (IFN-γ) and an inhibitory activity on the production of tumor necrosis factor (TNF).

Accordingly, the thiazole derivatives (I) and a pharmaceutically acceptable salt thereof can be used for prophylactic and/or therapeutic treatment of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, IFN-γ mediated diseases, TNF mediated diseases and the like in human beings or animals, and more particularly for

prophylactic and/or therapeutic treatment of inflammation and pain in joint and muscle [e.g. rheumatoid arthritis, rheumatois spondylitis, osteoarthritis, gouty arthritis, etc.], inflammatory skin condition [e.g. sunburn, eczema, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis (inflammation, pain and tumescence after operation or injury), pyrexia, pain and other conditions associated with inflammation, rejection by transplantation, systemic lupus erythematosus, scleroderma, polymyositis, polychondritis, periarteritis nodosa, ankylosing spondytis, inflammatory chronic renal condition [e.g. glomerulonephritis, membranous nephritis, etc.], rheumatic fever, Sjögren's syndrome, Behcet disease, thyroiditis, diabetes [e.g. diabetes mellitus type I, diabetes mellitus type II, etc.], dermatomyositis, hepatitis [e.g. acute hepatitis, chronic active hepatitis, etc.], myasthenia gravis, idiopathic sprue, Grave's disease, multiple sclerosis, primary billiary cirrhoris, Reiter's syndrome, autoimmune hematological disorders [e.g. hemolytic anemia, pure red cell anemia, idiopathic thrombocytopenia, aplastic anemia, etc.], uveitis, contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Wegner's granulomatosis, Hodgkin's disease, emphysema, chronic bronchiolitis, osteoporosis, eosinophilia, cystic fibrosis, pancreatitis, nephritis, atopic dermatitis, idiopathic sprue, endocrine ophthalmopathy, non infection uveitis, autoimmune keratitis (e.g. keratoconjunctivitis sicca, vernal keratoconjunctivitis, etc.), interstitial lung fibrosis, psoriatic arthritis, cancer cachexia, AIDS cachexia, thrombosis, chronic granulomutotic diseases, tuberculosis, leprosy, meurological inflammatory conditions,

graft versus host disease and atherosclerosis, shock (e.g. septic shock, hemorrhagic shock, burn shock, anaphylactic shock, etc.), and the like.

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the object compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous, intramuscular and intra-articular) administrations or insufflation.

The active ingredient may be used in admixture with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. And, if necessary, in addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be used.

The object compound (I) or a pharmaceutically acceptable salt thereof is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the diseases.

The pharmaceutical composition of the present invention can be prepared by the conventional method in this field of the art. If necessary, the technique generally used in this field of the art for improving the bioavailability of a drug can be applied to the pharmaceutical composition of the present invention.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous (including i.v. infusion), intramuscular, pulmonary, or oral administration, or insufflation including aerosols from metered dose inhalator, nebulizer or dry powder inhalator.

While the dosage of therapeutically effective amount of the object compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, the preferred daily dosage can generally be selected from the range of 0.001-100mg of the object compound (I) per kg weight of a human being or an animal, for the prophylactic and/or therapeutic treatment of aforesaid diseases in a human being or an animal.

The following preparations and examples are given only for the purpose of illustrating the present invention in more detail.

Preparation 1

A mixture of chloroacetyl chloride (1.96ml) and aluminum chloride (7.6g) in methylene chloride (20ml) was stirred at room temperature for 20 minutes. A solution of 3,4-dihydro-1-methyl-2(1H)-quinolinone (3.1g) in methylene chloride (10ml) was added dropwise to the above mixture. The whole mixture was refluxed for 7 hours, poured into ice, and extracted with methylene chloride. The obtained extract was dried over anhydrous magnesium sulfate and evaporated to give 6-(chloroacetyl)-3,4-dihydro-1-methyl-2(1H)-quinolinone (4.8g) as pale brown crystals.

^{1}H-NMR (DMSO-d_6, δ) : 2.60 (2H, t, J=7Hz), 2.96 (2H, t, J=7Hz), 3.29 (3H, s), 5.12(2H, s), 7.22 (1H, d, J=8Hz), 7.8-8.0 (2H,m)

Mass (m/z) : 238 (M + 1)$^+$

Example 1

A mixture of 6-(chloroacetyl)-3,4-dihydro-1-methyl-2(1H)-quinolinone (1.2g) and N-methylthiourea (0.46g) in ethanol (12ml) was refluxed for 1 hour. Ethyl acetate (13ml) was added, and the obtained precipitates were collected and washed with ethyl acetate to give 6-[2-(methylamino)thiazol-4-yl]-3,4-dihydro-1-methyl-2(1H)-quinolinone hydrochloride (1.1g) as pale brown crystals.

mp : 206-208℃

IR (Nujol, cm^{-1}) : 3300, 1680, 1630, 1510

^{1}H-NMR (DMSO-d_6, δ) : 2.57 (2H, t, J=7Hz), 2.92 (2H, t, J=7Hz), 3.04 (3H, s), 3.28(3H, s), 7.13 (1H, s), 7.17(1H,d, J=8Hz), 7.6-7.8(2H,m)

Mass (m/z) : 274 $(M + 1)^+$

Example 1-(1)

A mixture of 6-[2-(methylamino)thiazol-4-yl]-3,4-dihydro-1-methyl-2(1H)-quinolinone hydrochloride (0.9g) and lithium aluminum hydride (0.33g) in tetrahydrofuran (15ml) was stirred at 50℃ for 5 hours. Aqueous sodium hydroxide (4N; 8ml) was added dropwise to the cooled mixture, and the whole mixture was filtered through diatomaceous earth. The obtained filtrate was extracted with ethyl acetate, and the extract was dried and evaporated. The resultant residue was chromatographed (methylene chloride:methanol, 50:1) over slica gel and the product was recrystallized from ethanol to afford 6-[2-(methylamino)thiazol-4-yl]-1-methyl-1,2,3,4-tetrahydroquinoline (0.18g) as pale brown crystals.

mp : 140-142℃

IR (Nujol, cm^{-1}) : 3250, 1610, 1590, 1490

^{1}H-NMR ($CDCl_3$, δ) :1.8-2.0 (2H, m), 2.71 (2H, t, J=6Hz), 2.84 (3H, s), 2.85 (3H, d, J=4Hz), 3.20 (2H, t, J=6Hz), 6.54 (1H, d, J=9Hz), 6.65(1H, s), 7.3-7.5(3H, m)

Mass (m/z) : 260 $(M + 1)^+$

Example 2

The following compound was obtained in a similar manner to that of Example 1.

6-[2-(4-pyridyl)thiazol-4-yl]-3,4-dihydro-1-methyl-2(1H)-quinolinone

mp : 193-195℃

IR (Nujol, cm^{-1}) : 1660, 1600

^{1}H-NMR (DMSO-d_6, δ) : 2.60 (2H, t, J=7Hz), 2.97 (2H, t, J=7Hz), 3.30 (3H, s), 7.20 (1H,d, J=8Hz), 7.9-8.0 (4H, m), 8.28 (1H, s), 8.75(2H, d, J=6Hz)

Mass (m/z) : 322 $(M + 1)^+$

Example 2-(1)

The following compound was obtained in a similar manner to that of Example 1-(1).

6-[2-(4-pyridyl)thiazol-4-yl]-1-methyl-1,2,3,4-tetrahydroquinoline

mp : 132-134℃

IR (Nujol, cm^{-1}) : 1610, 1595, 1530

^{1}H-NMR (DMSO-d_6, δ) : 1.8-2.0 (2H, m), 2.78 (2H, t, J=6Hz), 2.89 (3H, s), 3.25(2H,t, J=6Hz), 6.64 (1H, d, J=9Hz), 7.6-8.0 (5H, m), 8.72(2H, d, J=6Hz)

Mass (m/z) : 308 $(M + 1)^+$

Preparation 2

The following compound was obtained in a similar manner to that

of Preparation 1.

5-(chloroacetyl)oxindole

^{1}H-NMR (DMSO-d_6, δ) : 3.57 (2H, s), 5.09 (2H, s), 6.93 (1H, d, J=8Hz), 7.8-8.0 (2H, m), 10.84 (1H, s)

Mass (m/z) : 210 $(M + 1)^+$

Example 3

The following compound was obtained in a similar manner to that of Example 1.

5-[2-(4-pyridyl)thiazol-4-yl]oxindole

mp : 272-275°C

IR (Nujol, cm^{-1}) : 1700, 1625, 1600

^{1}H-NMR (DMSO-d_6, δ) : 3.58 (2H, s), 6.92 (1H, d, J=9Hz), 7.9-8.0 (4H, m), 8.18 (1H, s), 8.73 (2H, d, J=6Hz), 10.54 (1H, s)

Mass (m/z) : 294 $(M + 1)^+$

Example 3-(1)

A mixture of 5-[2-(4-pyridyl)thiazol-4-yl]oxindole (1.5g) and sodium hydride (60%; 0.61g) in N,N-dimethylformamide (20ml) was stirred at room temperature for 1 hour. Iodomethane (1.05ml) was then added to the ice-cooled mixture.

The whole mixture was stirred at room temperature for 3 hours, poured into ice- water, and extracted with methylene chloride. The obtained extract was evaporated, and the residue was chromatographed (methylene chloride:ethyl acetate, 1:1) over silica gel. The product was recrystallized from ethanol to give 5-[2-(4-pyridyl)thiazol-4-yl]-1,3,3-trimethyloxindole (0.86g) as pale brown crystals.

mp : 207-208°C

IR (Nujol, cm^{-1}) : 1705, 1600

^{1}H-NMR (DMSO-d_6, δ) :1.35 (6H, s), 3.19 (3H, s), 7.13 (1H,d, J=8Hz), 7.9-8.1(4H,m), 8.25 (1H, s), 8.75 (2H, d, J=6Hz)

Mass (m/z) : 336 $(M + 1)^+$

Preparation 3

The following compound was obtained in a similar manner to that of Preparation 1.

5'-(chloroacetyl)-1'-methylspiro[cyclopropane-1,3'-oxindole]

^{1}H-NMR (DMSO-d_6, δ) :1.5-1.8 (4H, m), 3.27 (3H, s), 5.12 (2H, s), 7.22 (1H, d, J=8Hz), 7.67 (1H, d, J=2Hz), 7.97 (1H, dd, J=8, 2Hz)

Example 4

The following compound was obtained in a similar manner to that of Example 1.

1'-methyl-5'-[2-(4-pyridyl)thiazol-4-yl]spiro-[cyclopropane-1,3'-oxindole]

mp: 187-189°C

IR(Nujol, cm^{-1}) : 1710, 1625, 1600

^{1}H-NMR (DMSO-d_6, δ) :1.5-1.8 (4H, m), 3.27 (3H, s), 7.18 (1H, d, J=8Hz), 7.7-8.1 (4H, m), 8.20 (1H, s), 8.74 (2H, d, J=6Hz)

Preparation 4

The following compound was obtained in a similar manner to that of Preparation 1.

5-(chloroacetyl)-1-isopropyloxindole

^{1}H-NMR ($CDCl_3$, δ) :1.50 (6H, d, J=7Hz), 3.56 (2H, s), 4.64

(2H, s), 4.6-4.8 (1H, m), 7.07 (1H, d, J=8Hz), 7.8-8.0 (2H, m)

Mass (m/z) : 252 (M + 1)$^+$

Example 5

The following compound was obtained in a similar manner to that of Example 1.

1-isopropyl-5-[2-(4-pyridyl)thiazol-4-yl]oxindole

mp: 120-122℃

^{1}H-NMR (DMSO-d_6, δ) :1.43 (6H, d, J=7Hz), 3.63 (2H, s), 4.5-4.7 (1H, m), 7.26 (1H, d, J=9Hz), 7.9-8.0 (4H, m), 8.23 (1H, s), 8.74 (2H, d, J=6Hz)

Mass (m/z) : 336 (M + 1)$^+$

Example 5-(1)

A mixture of 1-isopropyl-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.2g) and sodium hydride (60%; 48mg) in N,N-dimethylformamide (1ml) was stirred at room temperature for 30 minutes. 1,2-dibromoethane (53μl) was added to the ice-cooled mixture. The whole mixture was stirred at room temperature for 2 hours and poured into ice- water. The obtained precipitates were collected and washed successively with water and ethanol to give 1'-isopropyl-5'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole] (0.13g) as a pale brown powder.

mp : 175-177℃

^{1}H-NMR (DMSO-d_6, δ) :1.46 (6H, d, J=7Hz), 1.5-1.8 (4H, m), 4.5-4.8 (1H,m), 7.35 (1H, d, J=8Hz), 7.7-8.0 (4H, m), 8.20 (1H, s), 8.74 (2H, d, J=6Hz)

Mass (m/z) : 362 (M + 1)$^+$

Preparation 5

The following compound was obtained in a similar manner to that of Preparation 1.

7-(chloroacetyl)-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR (DMSO-d_6, δ) : 2.1-2.3 (4H, m), 2.7-2.9 (2H, m), 5.14 (2H, s), 7.08 (1H, d, J=8Hz), 7.8-7.9 (2H, m), 9.90 (1H, s)

Mass (m/z) : 238 (M + 1)$^+$

Example 6

The following compound was obtained in a similar manner to that of Example 1.

7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 225°C

IR(KBr, cm^{-1}) : 3470, 1675, 1600, 1480

^{1}H-NMR (DMSO-d_6, δ) : 2.1-2.3 (4H, m), 2.7-2.9 (2H, m), 7.07 (1H, d, J=8Hz), 7.9-8.0 (4H, m), 8.28 (1H, s), 8.75 (2H, d, J=6Hz), 9.64 (1H, s)

Mass (m/z) : 322 (M + 1)$^+$

Example 6-(1)

A mixture of 7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (3.5g) and sodium hydride (60%; 0.78g) in N,N-dimethylformamide (15ml) was stirred at room temperature for 30 minutes. To the mixture, 2-iodopropane (2.2ml) was added, and the whole mixture was stirred at room temperature for 4 hours. The mixture was poured into ice- water, and extracted with ethyl acetate . The obtained extract was evaporated, and the oily residue was

chromatographed (methylene chloride:methanol, 50:1) over silica gel. The product was recrystallized from ethanol to give 1-isopropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (2.3g) as pale brown crystals.

mp:164-165℃

IR(KBr, cm^{-1}) : 1650, 1590, 1480

^{1}H-NMR ($CDCl_3$, δ) :1.11 (3H, d, J=7Hz), 1.48 (3H, d, J=7Hz), 1.9-2.5 (4H,m), 2.6-3.0 (2H, m), 4.7-5.0 (1H, m), 7.29 (1H, d, J=8Hz), 7.62 (1H, s), 7.8-8.0 (4H, m), 8.75 (2H, d, J=6Hz)

Mass (m/z) : 364 (M + 1)$^+$

Example 6-(1)-(1)

A mixture of 1-isopropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (750mg) and N-bromosuccinimide (733mg) in ethyl acetate (10ml) and tetrahydrofuran (10ml) was stirred at room temperature overnight. The reaction mixture was poured into water, extracted with ethyl acetate. The extract was dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed over silica gel eluting with a mixture of toluene and ethyl acetate (1:1). The product was precipitated with diisopropyl ether to afford 1-isopropyl-7-{[2-(4-pyridyl)-5-bromo]thiazol-4-yl}-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one as an amorphous powder.

^{1}H-NMR ($CDCl_3$, δ) : 1.1-1.2 (3H, m), 1.4-1.6 (3H, m), 1.8-2.4 (4H, m), 2.7-2.9 (2H, m), 4.7-5.0 (1H, m), 7.2-7.4 (1H, m), 7.8-8.0 (4H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 442 (M + 1)$^+$ 444 (M + 1)$^+$

Example 6-(1)-(1)-(1)

A mixture of 1-isopropyl-7-{[2-(4-pyridyl)-5-bromo]thiazol-4-yl}-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (300mg) and sodium

thiomethoxide (57mg) in N,N-dimethylformamide (2ml) was stirred at room temperature for 1 hour. The reaction mixture was poured into water, and extracted with ethyl acetate. The extract was washed with water and brine, dried over sodium sulfate, and evaporated in vacuo to give a residue. The residue was dissolved in ethyl acetate. A solution of 4N-hydrogenchloride in ethyl acetate (0.204ml) was added to the solution. The precipitates were collected by filtration to give 1-isopropyl-7-{[2-(4-pyridyl)-5-methylthio]thiazol-4-yl}-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride (201mg) as a yellow powder.

^{1}H-NMR (DMSO-d_6, δ) : 1.0-1.3 (3H, m), 1.3-1.5 (3H, m), 1.8-2.3 (4H, m), 2.6-2.8 (2H, m), 2.75 (3H, s), 4.5-4.8 (1H, m), 7.3-7.5 (1H, m), 7.7-7.8 (2H, m), 8.3-8.4 (2H, m), 8.9-9.0 (2H, m)

Mass (m/z) : 410 $(M + 1)^+$ (free)

Example 6-(1)-(2)

The following compound was obtained in a similar manner to that of Example 6-(1)-(1).

1-isopropyl-7-{[2-(4-pyridyl)-5-chloro]thiazol-4-yl}-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.0-1.3 (3H, m), 1.4-1.6 (3H, m), 1.8-2.1 (1H, m), 2.1-2.6 (3H, m), 2.6-3.0 (2H, m), 4.7-5.0 (1H, m), 7.2-7.4 (1H, m), 7.8-8.0 (2H, m), 8.4-8.5 (2H, m), 9.0-9.1 (2H, m)

Mass (m/z) : 398 $(M + 1)^+$

Example 6-(2)

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isobutyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-

benzazepin-2-one

mp: 153-155℃

^{1}H-NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7Hz), 1.6-2.4 (7H, m), 2.8-3.0 (2H, m), 7.28 (1H, d, J=8Hz), 7.61 (1H, s) 7.8-8.0 (4H, m), 8.7-8.9 (2H, m)

Mass (m/z) : 378 $(M + 1)^+$

Preparation 6

A solution of indoline (20g) and triethylamine (25.8ml) in tetrahydrofuran (10ml) was added dropwise to an ice-cooled solution of succinic anhydride (16.8g) in tetrahydrofuran (100ml). The mixture was stirred at room temperature for 3 hours and acidified with 1N HCl (230ml). The whole mixture was extracted with ethyl acetate, and the obtained extract was washed with brine, dried, and evaporated. The residue was washed with diisopropyl ether to give 4-(1-indolinyl)-4-oxobutanoic acid (20.8g) as a light pink powder.

mp:147-149℃

IR(KBr, cm^{-1}) : 1640, 1595

^{1}H-NMR ($CDCl_3$, δ) : 2.79 (4H, s), 3.23 (2H, t, J=8Hz), 4.09 (2H, t, J=8Hz), 7.0-7.3 (3H, m), 8.20 (1H, d, J=8Hz)

Mass (m/z) : 220 $(M + 1)^+$

Preparation 6-(1)

Oxalyl chloride (4.4ml) was added dropwise to an ice-cooled solution of 4-(1-indolinyl)-4-oxobutanoic acid (10g) and N,N-dimethylformamide (1 drop) in 1,2-dichloroethane (100ml). Then, aluminum chloride (30.4g) was added, and the whole mixture was stirred at 50℃ overnight. The mixture was poured into a mixture of ice water and ethyl acetate, and the insoluble product was removed by filtration. The resulted organic layer was dried and evaporated. The residue was

chromatographed (hexane:ethyl acetate, 5:3) over silica gel to give 1,9-ethylene-1,3,4,5-tetrahydro-2H-1-benzazepin-2,5-dione (1.5g) as a pale yellow powder.

mp:134-137℃

IR(KBr, cm^{-1}) : 1690, 1650, 1610

^{1}H-NMR ($CDCl_3$, δ) : 2.8-3.0 (4H, m), 3.16 (2H, t, J=9Hz), 4.25 (2H, t, J=9Hz), 7.11 (1H, t, J=8Hz),) 7.43 (1H, dd, J=8, 1Hz), 7.94 (1H, dd, J=8, 1Hz).

Mass (m/z) : 202 $(M + 1)^+$

Preparation 6-(1)-(1)

10% Pd-C (0.85g) was added to a solution of 1,9-ethylene-1,3,4,5-tetrahydro-2H-1-benzazepin-2,5-dione (0.95g) in acetic acid (13ml). Hydrogenation was carried out in a Parr apparatus at 50 psi for 7 hours. The catalyst used in the hydrogenation was removed by filtration and washed with ethyl acetate. The obtained filtrate was evaporated, and the residue was dissolved in ethyl acetate and washed with aqueous sodium bicarbonate. The resultant organic layer was dried and evaporated to give 1,9-ethylene-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (0.83g) as a pale yellow powder.

mp: 70-72℃

IR(KBr, cm^{-1}) : 1620, 1595, 1460

^{1}H-NMR ($CDCl_3$, δ) : 1.9-2.1 (2H, m), 2.7-3.2 (6H, m), 4.13 (2H, t, J=8Hz), 6.8-7.1 (3H, m)

Mass (m/z) : 188 $(M + 1)^+$

Preparation 6-(1)-(1)-(1)

The following compound was obtained in a similar manner to that of Preparation 1.

7-(chloroacetyl)-1,9-ethylene-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 170-173℃

IR(KBr, cm^{-1}) : 1675, 1640, 1600

^{1}H-NMR ($CDCl_3$, δ) : 1.9-2.1 (2H, m), 2.7-3.2 (6H, m), 4.1-4.3 (2H, m), 4.63 (2H, s) 7.6-7.7 (2H, m)

Mass (m/z) : 264 $(M + 1)^+$

Example 7

The following compound was obtained in a similar manner to that of Example 1.

1,9-ethylene-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 199-201℃

IR(KBr, cm^{-1}) : 1700, 1660, 1600, 1480

^{1}H-NMR ($CDCl_3$, δ) : 1.9-2.1 (2H, m), 2.8-3.2 (6H, m), 4.15 (2H, t, J=8Hz), 7.51 (1H, s), 7.6-7.9 (4H, m), 8.73 (2H, d, J=6Hz)

Mass (m/z) : 348 $(M + 1)^+$

Example 8-(1)

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-6-[2-(4-pyridyl)thiazol-4-yl]-3,4-dihydro-2(1H)-quinolinone

mp: 158.6-160.1℃

^{1}H-NMR ($CDCl_3$, δ) : 1.55 (6H, d, J=7Hz), 2.5-2.7 (2H, m), 2.8-3.0 (2H, m), 7.21 (1H, d, J=9Hz), 7.55 (1H, s), 7.7-8.0 (4H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 350 $(M + 1)^+$

Example 8-(2)

The following compound was obtained in a similar manner to that of Example 1-(1).

1-isopropyl-6-[2-(4-pyridyl)thiazol-4-yl]-1,2,3,4-tetrahydroquinoline dihydrochloride

mp: 251.6-253.6°C

IR(KBr, cm^{-1}) : 1629, 1513

^{1}H-NMR (DMSO-d_6, δ) : 1.0-1.3 (6H, m), 1.7-2.0 (2H, m), 2.7-2.9 (2H, m), 3.1.0-1.3 (6H, m), 1.7-2.0 (2H, m), 2.7-2.9 (2H, m),7.6-7.8 (2H, m), 8.33 (1H, s), 8.4-8.6 (2H, m), 8.9-9.1 (2H, m)

Mass (m/z) : 336 $(M + 1)^+$ (free)

Example 9

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isonicotinoylmethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.2-2.6 (4H, m), 3.0-3.2 (2H, m), 5.23 (2H, s), 7.18 (1H, d, J=8Hz), 7.60 (1H, s), 7.7-8.0 (6H, m), 8.6-8.8 (2H, m), 8.8-8.9 (2H, m)

Mass (m/z) : 441 $(M + 1)^+$

Example 10

A mixture of 7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (500mg) and sodium hydride (60%; 250mg) in N,N-dimethylformamide (8ml) was stirred at 0°C for 30 minutes, and

then stirred at room temperature for 20 minutes. 4-chloromethylpyridine hydrochloride (537mg) and sodium iodide (1.17g) were added to the reaction mixture at 0℃, and stirred at room temperature for 8 hours. The whole mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed successively with water twice and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (chloroform : methanol= 50:1) over silica gel. The product was precipitated with diisopropyl ether to afford 1-(4-pyridylmethyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (425mg) as pale yellow crystals.

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.5(4H, m), 2.6-2.8 (2H, m), 5.05 (2H, s), 7.1-7.3 (3H, m), 7.61 (1H, s), 7.8-8.0 (4H, m), 8.4-8.6 (2H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 413 $(M + 1)^+$

Example 11

The following compound was obtained in a similar manner to that of Example 10.

1-propionylmethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 180.5-184.0℃

^{1}H-NMR ($CDCl_3$, δ) : 1.12 (3H, t, J=7Hz), 2.1-2.5 (4H, m), 2.54 (2H, q, J=7Hz), 2.9-3.2 (2H, m), 4.60 (2H, s), 7.12 (1H, d, J=9Hz), 7.60 (1H, s), 7.8-8.0 (4H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 392 $(M + 1)^+$

Example 12

The following compound was obtained in a similar manner to that

of Example 10.

1-(3-pyridyl)methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 168.3-170.9℃

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.3 (2H, m), 2.3-2.5 (2H, m), 2.5-2.7 (2H, m), 5.08 (2H, s), 7.1-7.4 (2H, m), 7.57 (1H, s), 7.6-8.0 (5H, m), 8.4-8.6 (2H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 413 $(M + 1)^+$

Example 13

The following compound was obtained in a similar manner to that of Example 10.

1-(2-pyridyl)methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 163.2-164.4℃

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.5 (4H, m), 2.7-3.0 (2H, m), 5.18 (2H, s), 7.1-7.3 (1H, m), 7.3-7.5 (2H, m), 7.58 (1H, s), 7.5-7.7 (1H, m), 7.8-8.0 (4H, m), 8.4-8.6 (1H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 413 $(M + 1)^+$

Example 14

The following compound was obtained in a similar manner to that of Example 10.

1-(3-methoxybenzoyl)methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 84.4-88.0℃

^{1}H-NMR ($CDCl_3$, δ) : 2.2-2.6 (4H, m), 2.9-3.2 (2H, m), 3.84 (3H,

s), 5.29 (2H, s), 7.1-7.6 (5H, m), 7.60 (1H, s), 7.7-8.0 (4H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 470 (M + 1)$^+$

Example 15

The following compound was obtained in a similar manner to that of Example 10.

1-(1-adamantyl)carbonylmethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 119.0-122.1℃

^{1}H-NMR ($CDCl_3$, δ) : 1.6-2.3 (19H, m), 2.9-3.2 (2H, m), 4.76 (2H, s), 7.08 (1H, d, J=9Hz), 7.60 (1H, s), 7.8-8.0 (4H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 498 (M + 1)$^+$

Example 16

The following compound was obtained in a similar manner to that of Example 10.

1-pivaloylmethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 167.1-169.6℃

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (9H, s), 2.1-2.5 (4H, m), 2.9-3.2 (2H, m), 4.79 (2H, s), 7.09 (1H, d, J=9Hz), 7.60 (1H, s), 7.8-8.0 (4H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 420 (M + 1)$^+$

Example 17

The following compound was obtained in a similar manner to that

of Example 10.

1-[2-(dimethylamino)ethyl]-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one dihydrochloride

mp: 170.1-174.9℃

^{1}H-NMR (DMSO-d_6, δ) : 2.0-2.3 (4H, m), 2.6-2.9 (8H, m), 3.1-3.4 (2H, m), 4.1-4.3 (2H, m), 7.58 (1H, d, J=9Hz), 8.0-8.1 (2H, m), 8.4-8.6 (2H, m), 8.65(1H, s), 8.9-9.1 (2H, m)

Mass (m/z) : 393 $(M + 1)^+$ (free)

Example 18

The following compound was obtained in a similar manner to that of Example 10.

1-(2-methylthioethyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp: 217.7-222.2℃

^{1}H-NMR (DMSO-d_6, δ) : 2.03 (3H, s), 2.0-2.3 (4H, m), 2.5-2.7 (2H, m), 2.8-3.0 (2H, m), 3.9-4.2 (2H, m), 7.54 (1H, d, J=9Hz), 8.0-8.1 (2H, m), 8.48 (1H, d, J=6.6Hz), 8.60 (1H, s), 8.98 (1H, d, J=6.6Hz)

Mass (m/z) : 396 $(M + 1)^+$ (free)

Example 19

The following compound was obtained in a similar manner to that of Example 10.

1-(2-methoxyethyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp: 234.3-235.8℃

^{1}H-NMR (DMSO-d_6, δ) : 2.0-2.3 (4H, m), 2.5-2.9 (2H, m), 3.17

(3H, s), 3.3-3.5 (2H, m), 3.8-4.1 (2H, m), 7.53 (1H, d, J=9Hz), 8.0-8.1 (2H, m), 8.49 (2H, d, J=6.6Hz), 8.60 (1H, s), 8.99 (2H, d, J=6.6Hz)

Mass (m/z) : 380 $(M + 1)^+$ (free)

Example 20

The following compound was obtained in a similar manner to that of Example 10.

1-(ethoxycarbonyl)methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp: 216.0-217.2℃

^{1}H-NMR (DMSO-d_6, δ) : 1.19 (3H, t, J=7.1Hz), 2.0-2.4 (4H, m), 2.8-3.1 (2H, m), 4.11 (2H, q, J=7.1Hz), 4.57 (2H, s), 7.42 (1H, d, J=9Hz), 7.9-8.1 (2H, m), 8.50 (2H, d, J=6.5Hz), 8.61 (1H, s), 8.99 (2H, d, J=6.5Hz)

Mass (m/z) : 408 $(M + 1)^+$ (free)

Example 20-(1)

A mixture of 1-(ethoxycarbonyl)methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride (430mg) and 1N-aqueous sodium hydroxide (4.84ml) in 1,2-dimethoxyethane (10ml) was stirred at room temperature for 5 hours. The whole was poured into 1N-hydrochloric acid (3.87ml), extracted with ethyl acetate. The extract was washed successively with water and brine, dried over sodium sulfate, and evaporated. The product was precipitated with diisopropyl ether to give 1-(carboxymethyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (390mg) as a pale yellow powder.

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.5(4H, m), 2.9-3.2 (2H, m), 4.60 (2H, s), 7.2-7.5 (1H, m), 7.62 (1H, s), 7.8-8.0 (4H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 380 $(M + 1)^+$

Example 20-(1)-(1)

A mixture of 1-(carboxymethyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (150mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (91mg) and a 2M solution (0.395ml) of dimethylamine in tetrahydrofuran was stirred at room temperature for 2 hours. The whole was poured into water and extracted with ethyl acetate . The extract was dried over sodium sulfate and evaporated in vacuo to give an oil (68mg). The oil was precipitated with diisopropyl ether to afford 1-(N,N-dimethylcarbamoylmethyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (49mg) as a white powder.

mp: 116.6-119.2℃

^{1}H-NMR ($CDCl_3$, δ) : 1.5-1.8 (2H, m), 2.1-2.5 (4H, m), 2.99 (3H, s), 3.09 (3H, s), 4.62 (2H, s), 7.2-7.4 (1H, m), 7.58 (1H, s), 7.8-8.0 (4H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 407 $(M + 1)^+$

Example 21

The following compound was obtained in a similar manner to that of Example 10.

1-benzoylmethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 164.9-166.3℃

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.6 (4H, m), 3.0-3.2 (2H, m), 5.30 (2H, s), 7.19 (1H, d, J=8Hz), 7.4-7.7 (4H, m), 7.7-8.1 (6H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 440 $(M + 1)^+$

Example 22

The following compound was obtained in a similar manner to that of Example 10.

1-hexyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp: 213.0-215.2℃

^{1}H-NMR (DMSO-d_6, δ) : 0.7-0.9 (3H, m), 1.1-1.6 (8H, m), 2.0-2.3 (4H, m), 2.6-2.9 (2H, m), 3.7-4.0 (2H, m), 7.48 (1H, d, J=9Hz), 7.9-8.1 (2H, m), 8.4-8.6 (2H, m), 8.61 (1H, s), 8.9-9.1 (2H, m)

Mass (m/z) : 406 $(M + 1)^+$ (free)

Preparation 7

The following compound was obtained in a similar manner to that of Preparation 12.

1-(hydroxyimino)-4-methyl-1,2,3,4-tetrahydronaphthalene

^{1}H-NMR ($CDCl_3$, δ) : 1.29 (3H, d, J=7Hz), 1.6-1.8 (1H, m), 1.8-2.1 (1H, m), 2.8-3.0 (3H, m), 7.1-7.4 (3H, m), 7.8-7.9 (1H, m), 9.45 (1H, s)

Mass (m/z) : 176 $(M + 1)^+$

Preparation 7-(1)

The following compound was obtained in a similar manner to that of Preparation 12-(1).

5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 159.1-162.2℃

^{1}H-NMR ($CDCl_3$, δ) : 1.35 (3H, d, J=7Hz), 1.6-1.9 (1H, m), 2.2-

2.5 (3H, m), 3.0-3.3 (1H, m), 6.9-7.1 (1H, m), 7.1-7.4 (3H, m), 8.47 (1H, s)

Mass (m/z) : 176 $(M + 1)^+$

Preparation 7-(1)-(1)

The following compound was obtained in a similar manner to that of Preparation 5.

7-(chloroacetyl)-5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.3-1.5 (3H, m), 1.7-2.0 (1H, m), 2.2-2.6 (3H, m), 3.0-3.3 (1H, m), 4.70 (2H, s), 7.13 (1H, d, J=9Hz), 7.7-8.0 (2H, m), 9.08 (1H, s)

Mass (m/z) : 252 $(M + 1)^+$

Example 23

The following compound was obtained in a similar manner to that of Example 6.

5-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 225.6-229.7℃

^{1}H-NMR ($CDCl_3$, δ) : 1.48 (3H, d, J=7Hz), 1.6-2.2 (1H, m), 2.2-2.6 (3H, m), 3.0-3.4 (1H, m), 7.07 (1H, d, J=8Hz), 7.62 (2H, s), 7.7-8.0 (4H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 336 $(M + 1)^+$

Example 23-(1)

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-5-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.0-1.2 (4H, m), 1.3-1.6 (6H, m), 2.1-2.6 (4H, m), 2.9-3.2 (1H, m), 4.7-5.0 (1H, m), 7.29 (1H, d, J=9Hz), 7.65 (1H, s), 7.8-8.0 (4H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 378 (M + 1)$^+$

Preparation 8

The following compound was obtained in a similar manner to that of Preparation 12.

1-(hydroxyimino)-2-methyl-1,2,3,4-tetrahydronaphthalene

^{1}H-NMR ($CDCl_3$, δ) : 1.23 (3H, d, J=7Hz), 1.6-1.8 (1H, m), 1.8-2.2 (1H, m), 2.6-2.8 (1H, m), 2.8-3.1 (1H, m), 3.5-3.8 (1H, m), 7.1-7.4 (3H, m), 7.7-7.9 (1H, m), 8.46 (1H, br)

Mass (m/z) : 176 (M + 1)$^+$

Preparation 8-(1)

The following compound was obtained in a similar manner to that of Preparation 12-(1).

3-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.0-1.3 (3H, m), 1.8-3.2 (5H, m), 6.9-7.4 (4H, m), 8.18 (1H, br)

Mass (m/z) : 176 (M + 1)$^+$

Preparation 8-(1)-(1)

The following compound was obtained in a similar manner to that of Preparation 5.

7-(chloroacetyl)-3-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.0-1.2 (3H, m), 1.9-3.1 (5H, m), 4.67 (2H, s), 7.11 (1H, d, J=9Hz), 7.8-7.9 (2H, m), 8.68 (1H, s)

Mass (m/z) : 252 (M + 1)$^+$

Example 24

The following compound was obtained in a similar manner to that of Example 6.

3-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.13 (3H, d, J=6.5Hz), 1.9-3.1 (5H, m), 7.06 (1H, d, J=8Hz), 7.59 (1H, s), 7.8-8.0 (4H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 336 (M + 1)$^+$

Example 24-(1)

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-3-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 79.1-83.2℃

^{1}H-NMR ($CDCl_3$, δ) : 1.0-1.2 (6H, m), 1.48 (3H, d, J=6.8Hz), 1.8-3.0 (5H, m), 7.2-7.4 (1H, m), 7.63 (1H, s), 7.8-8.0 (4H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 378 (M + 1)$^+$

Preparation 9

The following compound was obtained in a similar manner to that of Preparation 12.

1-(hydroxyimino)-8-methyl-1,2,3,4-tetrahydronaphthalene

^{1}H-NMR ($CDCl_3$, δ) : 1.7-2.0 (2H, m), 2.33 (3H, s), 2.72 (2H, t, J=6Hz), 2.82 (2H, t, J=7Hz), 7.0-7.2 (2H, m), 7.70 (1H, s)

Mass (m/z) : 176 (M + 1)$^+$

Preparation 9-(1)

The following compound was obtained in a similar manner to that of Preparation 12-(1).

8-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.5 (4H, m), 2.32 (3H, s), 2.75 (2H, t, J=7Hz), 6.83 (1H, s), 6.93 (1H, d, J=7.6Hz), 7.08 (1H, d, J=7.6Hz), 8.51 (1H, s)

Mass (m/z) : 176 (M + 1)$^+$

Preparation 9-(1)-(1)

The following compound was obtained in a similar manner to that of Preparation 5.

7-(chloroacetyl)-8-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.2-2.5 (4H, m), 2.53 (3H, s), 2.84 (2H, t, J=7Hz), 4.63 (2H, s), 6.91 (1H, s), 7.53 (1H, s), 8.41 (1H, s)

Mass (m/z) : 252 (M + 1)$^+$

Example 25

The following compound was obtained in a similar manner to that of Example 6.

8-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.2-2.5 (4H, m), 2.53 (3H, s), 2.8-2.9 (2H, m), 6.95 (1H, s), 7.42 (1H, s), 7.55 (1H, s), 7.8-8.0 (2H, m), 8.32 (1H, s), 8.7-8.8 (2H, m)

Mass (m/z) : 336 (M + 1)$^+$

Example 25-(1)

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-8-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.15 (3H, d, J=7Hz), 1.48 (3H, d, J=7Hz), 1.8-2.1 (1H, m), 2.2-2.4 (3H, m), 2.53 (3H, s), 2.5-2.9 (2H, m), 4.7-4.9 (1H, m), 7.14 (1H, s), 7.46 (1H, s), 7.51 (1H, s), 7.8-8.0 (2H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 378 (M + 1)$^+$

Preparation 10

The following compound was obtained in a similar manner to that of Preparation 12.

1-(hydroxyimino)-5-methyl-1,2,3,4-tetrahydronaphthalene

^{1}H-NMR ($CDCl_3$, δ) : 1.8-2.0 (2H, m), 2.28 (3H, s), 2.69 (2H, t, J=6Hz), 2.82 (2H, t, J=7Hz), 7.0-7.2 (2H, m), 7.7-7.8 (1H, m)

Mass (m/z) : 176 (M + 1)$^+$

Preparation 10-(1)

The following compound was obtained in a similar manner to that of Preparation 12-(1).

6-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.4 (4H, m), 2.36 (3H, s), 6.8-6.9 (1H, m), 6.9-7.2 (3H,m), 8.37 (1H, s)

Mass (m/z) : 176 (M + 1)$^+$

Preparation 10-(1)-(1)

A mixture of chloroacetyl chloride (1.26g) and aluminum chloride (3.42g) in methylene chloride (24ml) was stirred at room temperature for 15 minutes. 6-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (1.5g) was added portionwise to the above mixture. The whole was refluxed for 6 hours, poured into ice, and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and evaporated to give a residue. The residue was chromatographed over silica gel with eluting a mixture of toluene and ethyl acetate to give the following compounds: (a) 7-(chloroacetyl)-6-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (1.03g) and (b) 9-(chloroacetyl)-6-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (0.442g) as colorless powder.

(a) 7-(chloroacetyl)-6-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.5 (4H, m), 2.46 (3H, s), 2.90 (2H, t, J=7Hz), 4.58 (2H, s), 6.95 (1H, d, J=8Hz), 7.40 (1H, d, J=8Hz), 8.65 (1H, s)

Mass (m/z) : 252 (M + 1)$^+$

(b) 9-(chloroacetyl)-6-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.4 (4H, m), 2.44 (3H, s), 4.65 (2H, s), 7.08 (1H, d, J=8Hz), 7.59 (1H, d, J=8Hz), 9.71 (1H, s)

Mass (m/z) : 252 $(M + 1)^+$

Example 26

The following compound was obtained in a similar manner to that of Example 6.

6-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.5 (4H, m), 2.44 (3H, s), 2.8-3.0 (2H, m), 6.95 (1H, d, J=8Hz), 7.36 (1H, s), 7.3-7.5 (1H, m), 7.8-8.0 (2H, m), 8.1 (1H, s), 8.6-8.8 (2H, m)

Mass (m/z) : 336 $(M + 1)^+$

Example 26-(1)

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-6-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.14 (3H, d, J=6.8Hz), 1.48 (3H, d, J=6.8Hz), 1.7-2.0 (1H, m), 2.1-2.8 (4H, m), 2.42 (3H, s), 4.7-4.9 (1H, m), 7.15 (1H, d, J=8Hz), 7.3-7.5 (2H, m), 7.8-8.0 (2H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 378 $(M + 1)^+$

Example 27

The following compound was obtained in a similar manner to that of Example 6.

6-methyl-9-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.4 (4H, m), 2.42 (3H, s), 2.8-3.0 (2H, m), 7.08 (1H, d, J=8Hz), 7.42 (1H, d, J=8Hz), 7.57 (1H, s), 7.8-7.9 (2H, m), 8.7-8.8 (2H, m), 9.60 (1H, s)

Mass (m/z) : 336 $(M + 1)^+$

Example 27-(1)

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-6-methyl-9-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 0.9-1.1 (6H, m), 1.7-1.9 (1H, m), 2.2-2.5 (2H, m), 2.41 (3H, s), 2.6-2.8 (2H, m), 2.8-3.0 (1H, m), 3.6-3.9 (1H, m), 7.1-7.3 (1H, m), 7.4-7.6 (2H, m), 7.8-8.0 (2H, m), 8.6-8.8 (2H, m)

Mass (m/z) : 378 $(M + 1)^+$

Preparation 11

The following compound was obtained in a similar manner to that of Preparation 12.

2,2-dimethyl-1-(hydroxyimino)-1,2,3,4-tetrahydronaphthalene

^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, s), 1.51 (3H, s), 1.6-1.7 (1H, m), 1.8-1.9 (1H, m), 2.7-2.8 (1H, m), 2.8-3.0 (1H, m), 7.0-7.4 (3H, m), 7.7-7.9, 8.4-8.6 (total 1H, m)

Mass (m/z) : 190 (M + 1)$^+$

Preparation 11-(1)

The following compound was obtaincd in a similar manner to that of Preparation 12-(1).

3,3-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.10 (6H, s), 1.9-2.1 (2H, m), 1.7-1.9 (2H, m), 6.8-7.3 (4H, m), 7.97 (1H, s)

Mass (m/z) : 190 (M + 1)$^+$

Preparation 11-(1)-(1)

The following compound was obtained in a similar manner to that of Preparation 5.

7-(chloroacetyl)-3,3-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.17 (6H, s), 2.05 (2H, t, J=7Hz) , 2.93 (2H, t, J=7Hz), 4.68 (2H, s), 7.02 (1H, d, J=9Hz), 7.7-7.9 (2H, m), 8.59 (1H, s)

Mass (m/z) : 266 (M + 1)$^+$

Example 28

The following compound was obtained in a similar manner to that of Example 6.

3,3-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp: 256.9~259.6℃

^{1}H-NMR ($CDCl_3$, δ) : 1.15 (6H, s), 2.09 (2H, t, J=7Hz) , 2.95 (2H,

t, J=7Hz), 6.94 (1H, d, J=8Hz), 7.57 (1H, s), 7.7-8.0 (4H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 350 (M + 1)$^+$

Example 28-(1)

The following compound was obtained in a similar manner to that of Example 6-(1).

3,3-dimethyl-1-isopropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 0.8-1.2 (6H, m), 1.2-1.5 (6H, m), 1.9-2.1 (2H, m), 2.7-2.9 (2H, m), 4.7-4.9 (1H, m), 7.24 (1H, d, J=9Hz), 7.55 (1H, s), 7.8-8.0 (4H, m), 8.9-9.1 (2H, m)

Mass (m/z) : 392 (M + 1)$^+$

Preparation 12

A mixture of 3,3-dimethyl-1-tetralone (3.0g), hydroxylamine hydrochloride (1.28g) and sodium acetate (1.51g) in methanol (10ml) was stirred at 60°C for 2 hours. Hydroxylamine hydrochloride (384mg) and sodium acetate (453mg) were added to the reaction mixture, and the whole was stirred under the same condition for 0.5 hour. The mixture was cooled to ambient temperature, and the resulted precipitates were removed by filtration. The filtrate was evaporated in vacuo. The residue was poured into water, and extracted with ethyl acetate. The organic layer was evaporated in vacuo to afford 3,3-dimethyl-1-(hydroxyimino)-1,2,3,4-tetrahydronaphthalene (2.83g) as a white powder.

^{1}H-NMR ($CDCl_3$, δ) : 1.03 (6H, s), 2.65 (2H, s), 2.67 (2H, s), 7.0-7.4 (3H, m), 7.6-8.0 (2H, m)

Mass (m/z) : 190 (M + 1)$^+$

Preparation 12-(1)

A mixture of phosphorus pentaoxide (11g) and phosphoric acid (11ml) was stirred at 100℃ for 0.5 hour. 3,3-dimethyl-1-(hydroxyimino) -1,2,3,4-tetrahydronaphthalene (2.8g) was added to the mixture. The whole was stirred at 100℃ for 2.5 hours and poured into ice-cooling water, and the resultant precipitates were collected and washed with water to give 4,4-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (2.12g) as a white powder.

^{1}H-NMR ($CDCl_3$, δ) : 1.13 (6H, s), 2.09 (2H, s), 2.56 (2H, s), 6.9-7.3 (4H, m), 8.47 (1H, s)

Mass (m/z) : 190 $(M + 1)^+$

Preparation 12-(1)-(1)

The following compound was obtained in a similar manner to that of Preparation 5.

7-(chloroacetyl)-4,4-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.17 (6H, s), 2.13 (2H, s) , 2.64 (2H, s), 4.69 (2H, s), 7.12 (1H, d, J=8Hz), 7.8-7.9 (2H, m), 8.94 (1H, s)

Mass (m/z) : 266 $(M + 1)^+$

Example 29

The following compound was obtained in a similar manner to that of Example 6.

4,4-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.19 (6H, s), 2.15 (2H, s) , 2.67 (2H, s), 7.08 (1H, d, J=9Hz), 7.61 (1H, s), 7.8-8.0 (4H, m), 8.12 (1H, s) , 8.7-8.9

(2H, m)

Mass (m/z) : 350 (M + 1)$^+$

Example 29-(1)

A mixture of 4,4-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (180mg) and sodium hydride (60%, 37mg) in N,N-dimethylformamide (3ml) was stirred at room temperature for 0.5 hour. 2-iodopropane was then added to the ice-cooled mixture. The reaction mixture was stirred at room temperature for 2 hours, poured into saturated aqueous sodium hydrogencarbonate, and extracted with ethyl acetate. The extract was washed successively with water and brine, dried over sodium sulfate, and evaporated in vacuo, and the residue was chromatographed over silica gel. The product was dissolved in ethyl acetate. 4N-hydrogen chloride in ethyl acetate (0.8ml) was added to the solution to appear pale yellow precipitates.

The precipitates were collected by filtration to give 4,4-dimethyl-1-isopropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride (98mg) as pale yellow powder.

^{1}H-NMR ($CDCl_3$, δ) : 0.86 (3H, s), 1.09 (3H, d, J=7Hz), 1.18 (3H, s) , 1.41 (3H, d, J=7Hz), 1.7-2.0 (2H, m), 2.3-2.7 (2H, m), 4.5-4.7 (1H, m), 7.39 (1H, d, J=8Hz), 7.9-8.1 (2H, m), 8.48 (2H, d, J=6.5Hz), 8.62 (1H, s), 8.99 (2H, d, J=6.5Hz)

Mass (m/z) : 392 (M + 1)$^+$

Preparation 13

The following compound was obtained in a similar manner to that of Preparation 12.

4,4-dimethyl-1-(hydroxyimino)-1,2,3,4-tetrahydronaphthalene

^{1}H-NMR ($CDCl_3$, δ) : 1.30 (6H, s), 1.76 (2H, t, J=7Hz), 2.90 (2H,

t, J=7Hz), 7.1-7.4 (3H, m), 7.8-8.0 (1H, m), 8.24 (1H, br)

Mass (m/z) : 190 (M + 1)$^+$

Preparation 13-(1)

The following compound was obtained in a similar manner to that of Preparation 12-(1).

5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.40 (6H, s), 2.0-2.2 (2H, m), 2.3-2.5 (2H, m), 6.9-7.05 (1H, m), 7.1-7.3 (2H, m), 7.3-7.5 (1H, m), 8.68 (1H, s)

Mass (m/z) : 190 (M + 1)$^+$

Preparation 13-(1)-(1)

The following compound was obtained in a similar manner to that of Preparation 5.

7-(chloroacetyl)-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.46 (6H, s), 2.1-2.2 (2H, m) , 2.4-2.6 (2H, m), 4.67 (2H, s), 7.10 (1H, d, J=8Hz), 7.7-7.9 (1H, m), 8.0-8.1 (1H, m), 9.10 (1H, s)

Mass (m/z) : 266 (M + 1)$^+$

Example 30

The following compound was obtained in a similar manner to that of Example 6.

5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.51 (6H, s), 2.1-2.3 (2H, m) , 2.4-2.6 (2H,

m), 7.06 (1H, d, J=8Hz), 7.58 (1H, s), 7.7-8.0 (3H, m), 8.0-8.1 (1H, m), 8.33 (1H, s), 8.7-8.8 (2H, m)

Mass (m/z) : 350 (M + 1)$^+$

Example 30-(1)

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.02 (3H, d, J=7Hz), 1.35 (3H, s), 1.5-1.6 (6H, m), 1.8-2.0 (1H, m), 2.1-2.5 (3H, m), 4.6-4.9 (1H, m), 7.27 (1H, d, J=8Hz), 7.63 (1H, s), 7.8-8.0 (3H, m), 8.0-8.1 (1H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 392 (M + 1)$^+$

Preparation 14

The following compound was obtained in a similar manner to that of Preparation 5.

7-(2-chloropropionyl)-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.75 (3H, d, J=6.6Hz), 2.2-2.5 (4H, m) , 2.89 (2H, t, J=7Hz), 5.24 (1H, q, J=6.6Hz), 7.12 (1H, d, J=9Hz), 7.8-8.0 (2H, m), 9.11 (1H, s)

Mass (m/z) : 252 (M + 1)$^+$

Example 31

The following compound was obtained in a similar manner to that of Example 6.

7-{[2-(4-pyridyl)-5-methyl]thiazol-4-yl}-1,3,4,5-tetrahydro-2H-

1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 2.1-2.5 (4H, m), 2.66 (3H, s), 2.8-3.0 (2H, m), 7.0-7.2 (1H, m), 7.5-8.1 (5H, m), 8.71 (2H, m)

Mass (m/z) : 336 $(M + 1)^+$

Example 31-(1)

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-7-{[2-(4-pyridyl)-5-methyl]thiazol-4-yl}-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp: 228.1-230.5°C

^{1}H-NMR (DMSO-d_6, δ) : 1.0-1.3 (3H, m), 1.3-1.5 (3H, m), 1.8-2.3 (4H, m), 2.6-2.9 (2H, m), 2.75 (3H, s), 4.5-4.8 (1H, m), 7.40 (1H, d, J=9Hz), 7.7-7.8 (2H, m), 8.3-8.5 (2H, m), 8.9-9.0 (2H, m)

Mass (m/z) : 378 $(M + 1)^+$ (free)

Preparation 15

The following compounds were obtained in a similar manner to that of Preparation 1.

(1) 1-isopropyl-7-(chloroacetyl)-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

^{1}H-NMR ($CDCl_3$, δ) : 1.0-1.3 (3H, m), 1.4-1.6 (3H, m), 1.8-2.4 (4H, m), 2.6-3.0 (2H, m), 4.70 (2H, s), 4.7-4.9 (1H, m), 7.2-8.0 (3H, m)

Mass (m/z) : 280 $(M+1)^+$

(2) 1-isopropyl-8-(chloroacetyl)-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.09 (3H, d, J=7 Hz), 1.49 (3H, d, J=7 Hz),

1.8-2.5 (4H, m), 2.6-3.0 (2H, m), 4.67 (2H, d, J=3 Hz), 4.7-4.9 (1H, m), 7.34 (1H, d, J=8 Hz), 7.7-7.9 (2H, m)

Mass (m/z) : 280 $(M+1)^+$

Example 32

The following compound was obtained in a similar manner to that of Example1.

1-isopropyl-8-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 166-167℃

NMR ($CDCl_3$, δ) : 1.15 (3H, d, J=7 Hz), 1.55 (3H, d, J=7 Hz), 1.8-2.5 (4H, m), 2.5-3.0 (2H, m), 4.7-5.0 (1H, m), 7.29 (1H, d, J=8 Hz), 7.61 (1H, s), 7.7-8.0 (4H, m), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 364 $(M+1)^+$

Example 33

The following compound was obtained in a similar manner to that of Example 1.

1-isopropyl-7-[2-(3-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp : 192-195℃

NMR (DMSO-d_6, δ) : 1.0-1.2 (3H, m), 1.3-1.5 (3H, m), 1.8-2.3 (4H, m), 2.6-2.9 (2H, m), 4.5-4.8 (1H, m), 7.37 (1H, d, J=9 Hz), 7.7-8.1 (3H, m), 8.34 (1H, s), 8.6-8.9 (2H, m), 9.33 (1H, s)

Mass (m/z) : 364 $(M+1)^+$

Example 34

The following compound was obtained in a similar manner to that

of Example 1.

1-isopropyl-7-[2-(2-chloro-5-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 149-150°C

NMR ($CDCl_3$, δ) : 1.10 (3H, d, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.8-2.5 (4H, m), 2.6-3.0 (2H, m), 4.7-5.0 (1H, m), 7.2-7.5 (2H, m), 7.57 (1H, s), 7.8-8.0 (2H, m), 8.2-8.4 (1H, m), 9.02 (1H, d, J=2 Hz)

Mass (m/z) : 398 $(M+1)^+$

Example 35

A mixture of 1-isopropyl-7-[2-(2-chloro-5-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (0.15 g) and formic hydrazide (0.23 g) in ethanol (4 ml) was heated at 200°C for 8 hours in a steel bomb. The resultant mixture was dissolved in ethyl acetate, washed successively with water and aqueous sodium hydrogencarbonate , dried, and evaporated. The residue was chromatographed [started from ethyl acetate and went finally to a mixture of ethyl acetate and methanol (10:1)] over silica gel to give the following two compounds.

(1) 1-isopropyl-7-[2-(2-amino-5-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (22 mg, pale brown powder)

mp : 195-200°C

NMR ($CDCl_3$, δ) : 1.10 (3H, d, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.8-2.5 (4H, m), 2.6-3.0 (2H, m), 4.7-5.0 (1H, m), 5.16 (2H, s), 6.65 (1H, d, J=9 Hz), 7.2-7.3 (1H, m), 7.43 (1H, s), 7.8-8.2 (3H, m), 8.69 (1H, d, J=2 Hz).

Mass (m/z) : 379 $(M+1)^+$

(2) 1-isopropyl-7-{(2-[1,2,4]triazolo[4,3-a]pyridin-6-

yl)thiazole-4-yl}-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (18 mg, pale brown powder)

mp : 188-191℃

NMR ($CDCl_3$, δ) : 1.0-1.2 (3H, m), 1.49 (3H, d, J=6 Hz), 1.8-2.5 (4H, m), 2.6-3.0 (2H, m), 4.7-5.0 (1H, m), 7.30 (1H, d, J=8 Hz), 7.60 (1H, s), 7.8-8.0 (4H, m), 9.01 (2H, s)

Mass (m/z) : 404 $(M+1)^+$

Example 36

The following compound was obtained in a similar manner to that of Example 1-(1).

6-(2-aminothiazol-4-yl)-1,2,3,4-tetrahydroquinoline

mp : 132-134℃

IR (Nujol) : 3350, 3150, 1650, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-1.9 (2H, m), 2.67 (2H, t, J=6 Hz), 3.1-3.3 (2H, m), 5.72 (1H, s), 6.38 (1H, d, J=9 Hz), 6.52 (1H, s), 6.85 (2H, s), 7.2-7.3 (2H, m)

Mass (m/z) : 232 $(M+1)^+$

Example 37

The following compound was obtained in a similar manner to that of Example1.

1-methyl-6-(2-aminothiazol-4-yl)-3,4-dihydro-2(1H)-quinolinone hydrochloride

mp : 231-234℃ (dec.)

IR (Nujol) : 3250, 1650, 1620, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 2.58 (2H, t, J=7 Hz), 2.92 (2H, t, J=7 Hz), 3.28 (3H, s), 7.15 (1H, s), 7.18 (1H, d, J=9 Hz), 7.6-7.8 (2H, m)

Mass (m/z) : 260 $(M+1)^+$

Example 38

The following compound was obtained in a similar manner to that of Example1-(1).

1-methyl-6-(2-aminothiazol-4-yl)-1,2,3,4-tetrahydroquinoline dihydrochloride

mp : 268-273℃ (dec.)

IR (Nujol) : 3450, 3300, 2600, 1620, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.0 (2H, m), 2.73 (2H, t, J=6 Hz), 2.91 (3H, s), 3.28 (2H, t, J=6 Hz), 5.2 (3H, broad), 6.68 (1H, d, J=8 Hz), 6.90 (1H, s), 7.3-7.5 (2H, m), 9.2 (1H, broad)

Mass (m/z) : 246 $(M+1)^+$

Example 39

The following compound was obtained in a similar manner to that of Example 1.

6-[2-(methylamino)thiazol-4-yl]-3,4-dihydro-2(1H)-quinolinone hydrochloride

mp : 298-301℃ (dec.)

IR (Nujol) : 3220, 1680, 1625, 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 2.48 (2H, t, J=7 Hz), 2.92 (2H, t, J=7 Hz), 3.03 (3H, s), 6.93 (1H, d, J=8 Hz), 7.06 (1H, s), 7.5-7.7 (2H, m), 10.25 (1H, s)

Mass (m/z) : 260 $(M+1)^+$

Example 40

The following compound was obtained in a similar manner to that

of Example 1-(1).

6-[2-(methylamino)thiazol-4-yl]-1,2,3,4-tetrahydroquinoline

mp : 157-159℃

IR (Nujol) : 3450, 3200, 1615, 1590, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-1.9 (2H, m), 2.68 (2H, t, J=6 Hz), 2.84 (3H, d, J=5 Hz), 3.18 (2H, t, J=5 Hz), 5.81 (1H, broad), 6.39 (1H, d, J=9 Hz), 6.58 (1H, s), 7.2-7.5 (3H, m)

Mass (m/z) : 246 $(M+1)^+$

Example 41

The following compound was obtained in a similar manner to that of Example 1.

6-[2-(4-pyridyl)thiazol-4-yl]-3,4-dihydro-2(1H)-quinolinone

mp : 284-288℃

IR (Nujol) : 1690, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.50 (2H, t, J=8 Hz), 2.98 (2H, t, J=8 Hz), 6.95 (1H, d, J=8 Hz), 7.8-8.0 (4H, m), 8.19 (1H, s), 8.74 (2H, d, J=6 Hz), 10.21 (1H, s)

Mass (m/z) : 308 $(M+1)^+$

Example 42

The following compound was obtained in a similar manner to that of Example 1- (1).

6-[2-(4-pyridyl)thiazol-4-yl]-1,2,3,4-tetrahydroquinoline -

mp : 165-167℃

IR (Nujol) : 3250, 1610, 1590. 1530 cm^{-1}.

NMR (DMSO-d_6, δ) : 1.7-1.9 (2H, m), 2.74 (2H, t, J=6 Hz), 3.1-

3.3 (2H, m), 5.96 (1H, s), 6.50 (1H, d, J=9 Hz), 7.5-7.6 (2H, m), 7.89 (1H, s), 7.93 (2H, d, J=6 Hz), 8.71 (2H, d, J=6 Hz)

Mass (m/z) : 294 $(M+1)^+$

Example 43

A mixture of 1-methyl-6-[2-(4-pyridyl)thiazol-4-yl]-3,4-dihydro-2(1H)-quinolinone (0.6 g) and m-chloroperbenzoic acid (80 % ; 0.42 g) in methylene chloride (30 ml) was stirred at room temperature for 5 hours. The resultant mixture was washed with aqueous sodium hydrogencarbonate , dried, and evaporated. The residue was recrystallized from ethanol to give 4-[4-(1-methyl-2-oxo-3,4-dihydro-1H-quinolin-6-yl)thiazol-2-yl]pyridine 1-oxide (0.38 g) as pale brown crystals.

mp : 210-212°C

IR (Nujol) : 3500, 1660, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 2.60 (2H, t, J=7 Hz), 2.97 (2H, t, J=7 Hz), 3.30 (3H, s), 7.19 (1H, d, J=9 Hz), 7.9-8.4 (7H, m)

Mass (m/z) : 338 $(M+1)^+$

Preparation 16

The following compound was obtained in a similar manner to that of Preparation 1.

4-methyl-6-(chloroacetyl)-2H-1,4-benzothiazine-3(4H)-one

NMR (DMSO-d_6, δ) : 3.41 (3H, s), 3.61 (2H, s), 5.23 (2H, s), 7.5-7.8 (3H, m)

Mass (m/z) : 256 $(M+1)^+$

Example 44

The following compound was obtained in a similar manner to that

of Example 1.

4-methyl-6-[2-(4-pyridyl)thiazol-4-yl]-2H-1,4-benzothiazine-3-(4H)-one

mp : 254-256°C

IR (Nujol) : 1670, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.47 (3H, s), 3.58 (2H, s), 7.53 (1H, d, J=8 Hz), 7.7-8.1 (4H, m), 8.49 (1H, s), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 340 $(M+1)^+$

Example 45

The following compound was obtained in a similar manner to that of Example 1-(1).

4-methyl-6-[2-(4-pyridyl)thiazol-4-yl]-3,4-dihydro-2H-1,4-benzothiazine

mp : 113-115°C

IR (Nujol) : 1600, 1565 cm^{-1}

NMR (DMSO-d_6, δ) : 3.02 (3H, s), 3.1-3.2 (2H, m), 3.5-3.6 (2H, m), 7.06 (1H, d, J=8 Hz), 7.2-7.4 (2H, m), 7.96 (2H, d, J=6 Hz), 8.27 (1H, s), 8.73 (2H, d, J=6 Hz)

Mass (m/z) : 326 $(M+1)^+$

Preparation 17

The following compound was obtained in a similar manner to that of Preparation 1.

1-acetyl-5-(chloroacetyl)indoline

NMR (DMSO-d_6, δ) : 2.20 (3H, s), 3.19 (2H, t, J=9 Hz), 4.16 (2H, t, J=9 Hz), 5.10 (2H, s), 7.8-8.2 (3H, m)

Mass (m/z) : 238 $(M+1)^+$

Example 46

The following compound was obtained in a similar manner to that of Example 1.

1-acetyl-5-[2-(4-pyridyl)thiazol-4-yl]indoline

mp : 194-196°C

IR (Nujol) : 1660, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 2.19 (3H, s), 3.23 (2H, t, J=9 Hz), 4.15 (2H, t, J=9 Hz), 7.8-8.2 (5H, m), 8.23 (1H, s), 8.74 (2H, d, J=6 Hz)

Mass (m/z) : 322 $(M+1)^+$

Example 47

A mixture of 1-acetyl-5-[2-(4-pyridyl)thiazol-4-yl]indoline (0.5 g) and concentrated hydrochloric acid (5 ml) was refluxed for 5 hours. The solvent was evaporated and the residue was washed with ethanol to give 5-[2-(4-pyridyl)thiazol-4-yl]indoline dihydrochloride (0.43 g) as a pale brown powder.

mp : 271-275°C

IR (Nujol) : 3340, 2500, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 3.26 (2H, t, J=8 Hz), 3.74 (2H, t, J=8 Hz), 7.41 (1H, d, J=8 Hz), 8.0-8.2 (2H, m), 8.40 (2H, d, J=6 Hz), 8.56 (1H, s), 8.95 (2H, d, J=6 Hz)

Mass (m/z) : 280 $(M+1)^+$

Example 48

The following compound was obtained in a similar manner to that of Example 6-(1).

1-(2-propynyl)-5-[2-(4-pyridyl)thiazol-4-yl]indoline

mp : 136-138℃

IR (Nujol) : 3180, 1615, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.9-3.2 (3H, m), 3.42 (2H, t, J=8 Hz), 4.06 (2H, s), 6.73 (1H, d, J=9 Hz), 7.7-8.0 (4H, m), 8.05 (1H, s), 8.73 (2H, d, J=6 Hz)

Mass (m/z) : 318 $(M+1)^+$

Example 49

Methanesulfonyl chloride (39.6μl) was added to a solution of 5-[2-(4-pyridyl)thiazol-4-yl]indoline dihydrochloride (0.15g) in pyridine (3 ml). The mixture was stirred overnight at room temperature and evaporated. The residue was dissolved in a mixture of methylene chloride and water. The resultant organic layer was separated, dried, and evaporated. The residue was recrystallized from ethanol to afford 1-(methanesulfonyl)-5-[2-(4-pyridyl)thiazol-4-yl]indoline (0.10 g) as pale yellow crystals.

mp : 199-201℃

IR (Nujol) : 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.05 (3H, s), 3.21 (2H, t, J=8 Hz), 4.00 (2H, t, J=8 Hz), 7.35 (1H, d, J=8 Hz), 7.9-8.0 (4H, m), 8.25 (1H, s), 8.74 (2H, d, J=6 Hz)

Mass (m/z) : 358 $(M+1)^+$

Example 50

The following compound was obtained in a similar manner to that of Example 1.

1'-methyl-5'-[2-(3-pyridyl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole]-hydrochloride

mp : 194-198℃

IR (Nujol) : 3400, 2550, 1690, 1630, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.8 (4H, m), 3.27 (3H, s), 7.18 (1H, d, J=8 Hz), 7.7-8.1 (3H, m), 8.21 (1H, s), 8.6-8.9 (2H, m), 9.36 (1H, d, J=2 Hz)

Mass (m/z) : 334 $(M+1)^+$

Example 51

The following compound was obtained in a similar manner to that of Example 43.

4-{4-(1'-methylspiro[cyclopropane-1,3'-oxindol-5'-yl])thiazol-2-yl}pyridine 1-oxide

mp : 232-235℃

IR (Nujol) : 1710, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.8 (4H, m), 3.26 (3H, s), 7.18 (1H, d, J=8 Hz), 7.7-8.1 (4H, m), 8.15 (1H, s), 8.32 (2H, d, J=5 Hz)

Mass (m/z) : 350 $(M+1)^+$

Example 52

A mixture of 1'-methyl-5'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole]hydrochloride (0.16 g), imidazole (1 g), dioxane (5 ml) and water (1 ml) was heated at 200℃ for 7 hours in a steel bomb. To the resultant mixture were added methylene chloride and water, and the organic layer was separated, dried, and evaporated. The residue was recrystallized from ethanol to give 1-methyl-3-[2-(1-imidazolyl)ethyl]-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (64 mg) as pale brown crystals.

mp : 204-206℃

IR (Nujol) : 1700, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.2-2.5 (2H, m), 3.15 (3H, s), 3.60 (1H, t,

J=6 Hz), 4.20 (2H, t, J=7 Hz), 6.89 (1H, s), 7.12 (1H, d, J=8 Hz), 7.21 (1H, s), 7.60 (1H, s), 7.9-8.1 (4H, m), 8.26 (1H, s), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 402 $(M+1)^+$

Example 53

The following compound was obtained in a similar manner to that of Example 1.

1'-methyl-5'-[2-(2-chloro-4-pyridyl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole]

mp : 261-263℃

IR (Nujol) : 1715, 1625, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.8 (4H, m), 3.27 (3H, s), 7.18 (1H, d, J=8 Hz), 7.7-8.1 (4H, m), 8.27 (1H, s), 8.57 (2H, d, J=5 Hz)

Mass (m/z) : 368 $(M+1)^+$

Example 54

A mixture of 1'-methyl-5'-[2-(2-chloro-4-pyridyl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole] (0.2 g) and sodium methoxide (294 mg) in toluene (5 ml) was refluxed overnight. To the resultant mixture were added methylene chloride and water, and the organic layer was separated, dried, and evaporated. The residue was recrystallized from ethanol to give 1'-methyl-5'-[2-(2-methoxy-4-pyridyl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole] (0.14 g) as off-white crystals.

mp : 155-157℃

IR (Nujol) : 1725, 1615, 1560 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.8 (4H, m), 3.26 (3H, s), 3.93 (3H, s), 7.17 (1H, d, J=8 Hz), 7.3-8.1 (4H, m), 8.18 (1H, s), 8.32 (1H, d, J=5 Hz)

Mass (m/z) : 364 $(M+1)^+$

Example 55

A mixture of 1'-methyl-5'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole] (0.7 g) and methyl iodide (1.3 ml) in ethanol (21 ml) and tetrahydrofuran (21 ml) was stirred at 40°C for 20 hours. The resultant mixture was cooled to afford 1-methyl-4-{4-(1'-methylspiro[cyclopropane-1,3'-oxindol-5'-yl])thiazol-2-yl}pyridinium iodide (0.74 g) as yellow crystals.

mp : > 300°C

IR (Nujol) : 1700, 1635, 1525 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.8 (4H, m), 3.28 (3H, s), 4.37 (3H, s), 7.22 (1H, d, J=8 Hz), 7.7-8.1 (2H, m), 8.52 (1H, s), 8.69 (2H, d, J=7 Hz), 9.06 (2H, d, J=7 Hz)

Mass (m/z) : 348, 334

Example 56

Sodium borohydride (0.29 g) was added portionwise at -5°C to a suspension of 1-methyl-4-{4-(1'-methylspiro[cyclopropane-1,3'-oxindol-5'-yl])thiazol-2-yl}pyridinium iodide (0.6 g) in methanol (12 ml). The mixture was stirred at 0°C for 1 hour and then at room temperature overnight. To the resultant mixture was added water, and extracted with methylene chloride. The organic extracts were dried and evaporated, and the residue was chromatographed [a mixture of methylene chloride and methanol (20:1)] over silica gel. The product was treated with excess hydrogen chloride in ethyl acetate to afford 1'-methyl-5'-[2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole]hydrochloride (174 mg) as a pale brown powder.

mp : > 300°C

IR (KBr) : 3400, 2700, 2600, 1690, 1625 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.8 (4H, m), 2.8-3.1 (5H, m), 3.25 (3H,

s), 3.5-4.1 (4H, m), 6.66 (1H, s), 7.15 (1H, d, J=8 Hz), 7.6-8.0 (2H, m), 7.98 (1H, s), 10.8 (1H, broad)

Mass (m/z) : 352 $(M+1)^+$

Example 57

A solution of 1'-methyl-5'-[2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole]hydrochloride (0.13 g), 1,2,2,6,6-pentamethylpiperidine (0.30 ml) and 1-chloroethyl chloroformate (0.29 ml) in 1,2-methylene chloride (4.2 ml) was refluxed for 1.5 hours. After evaporation, the residue was extracted with ethyl acetate, and the extracts were evaporated. The residue was chromatographed [a mixture of methylene chloride and ethyl acetate (3:1)] over silica gel to give 1'-methyl-5'-{2-[1-(1-chloroethoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]thiazol-4-yl}spiro[cyclopropane-1,3'-oxindole] (81 mg) as a pale brown oil.

NMR ($CDCl_3$, δ) : 1.5-1.9 (7H, m), 2.7-2.9 (2H, m), 3.33 (3H, s), 3.7-3.8 (2H, m), 4.2-4.3 (2H, m), 6.7-7.0 (3H, m), 7.2-7.9 (3H, m)

Example 58

A mixture of 1'-methyl-5'-{2-[1-(1-chloroethoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]thiazol-4-yl}spiro[cyclopropane-1,3'-oxindole-5'-yl] (80 mg) and hydrogen chloride in ethyl acetate (4N, 2 ml) in methanol (5 ml) was refluxed for 1 hour, and then evaporated. The residue was washed with a mixture of ethyl acetate, ethanol and diisopropyl ether to afford 1'-methyl-5'-[2-(1,2,3,6-tetrahydropyridin-4-yl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole]hydrochloride (61 mg) as a yellow powder.

mp : > 300°C

IR (KBr) : 3400, 2700, 2600, 1715, 1620, 1560, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.8 (4H, m), 2.8-3.0 (2H, m), 3.25 (3H,

s), 3.3-3.5 (2H, m), 3.7-4.0 (2H, m), 6.66 (1H, s), 7.15 (1H, d, J=8 Hz), 7.6-8.0 (2H, m), 7.97 (1H, s), 9.2 (2H, broad)

Mass (m/z) : 338 $(M+1)^+$

Preparation 18

To a mixture of imidazo[1,2-a]pyrazine-2-carbonitrile (1.23 g), triethylamine (1.19 ml), pyridine (10 ml), methanol (5 ml), and N,N-dimethylformamide (5 ml) was bubbled hydrogen sulfide for 2 hours. The reaction mixture was stirred overnight, and poured into ice-water (150 ml). The resultant precipitates were collected and washed with water to give imidazo[1,2-a]pyrazine-2-thiocarboxamide (1.0 g) as a pale brown powder.

NMR (DMSO-d_6, δ) : 7.97 (1H, d, J=5 Hz), 8.61 (1H, dd, J=5, 1 Hz), 8.68 (1H, s), 9.12 (1H, d, J=1 Hz), 9.66 (1H, s), 9.94 (1H, s)

Mass (m/z) : 179 $(M+1)^+$

Example 59

The following compound was obtained in a similar manner to that of Example 1.

1'-methyl-5'-[2-(imidazo[1,2-a]pyrazin-2-yl)thiazol-4-yl]spiro[cyclopropane-1,3'-oxindole]hydrochloride

mp : 177-180℃

IR (Nujol) : 3450, 2700, 1710, 1620, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-1.8 (4H, m), 3.27 (3H, s), 7.19 (1H, d, J=8 Hz), 7.7-8.1 (3H, m), 8.09 (1H, s), 8.6-8.8 (2H, m), 9.20 (1H, s)

Mass (m/z) : 374 $(M+1)^+$.

Example 60

The following compound was obtained in a similar manner to that

of Example 1.

1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]oxindole

mp : 187-188°C

IR (Nujol) : 1720, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.17 (3H, s), 3.65 (2H, s), 7.08 (1H, d, J=8 Hz), 7.9-8.1 (4H, m), 8.23 (1H, s), 8.73 (2H, d, J=6 Hz)

Mass (m/z) : 308 $(M+1)^+$

Example 61

The following compound was obtained in a similar manner to that of Example 5-(1).

1'-methyl-5'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclopentane-1,3'-oxindole]

mp : 192-193°C

IR (Nujol) : 1705, 1613, 1594 cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.1 (8H, m), 3.18 (3H, s), 7.10 (1H, d, J=8 Hz), 7.9-8.1 (4H, m), 8.30 (1H, s), 8.74 (2H, d, J=6 Hz)

Mass (m/z) : 362 $(M+1)^+$

Example 62

The following compound was obtained in a similar manner to that of Example 5-(1).

1'-methyl-5'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclobutane-1,3'-oxindole]

mp : 179-180°C

IR (Nujol) : 1695, 1617, 1598 cm^{-1}

NMR (DMSO-d_6, δ) : 2.2-2.6 (6H, m), 3.16 (3H, s), 7.07 (1H, d,

J=8 Hz), 7.9-8.1 (3H, m), 8.30 (1H, d, J=2 Hz), 8.33 (1H, s), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 348 $(M+1)^+$

Example 63

The following compound was obtained in a similar manner to that of Example 1-(1).

(1) 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]indole

mp : 185-186℃

IR (Nujol) : 1595, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 3.83 (3H, s), 6.53 (1H, d, J=3 Hz), 7.38 (1H, d, J=3 Hz), 7.53 (1H, d, J=8 Hz), 7.8-8.1 (3H, m), 8.21 (1H, s), 8.31 (1H, d, J=1 Hz), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 292 $(M+1)^+$

(2) 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]indoline

mp : 121-122℃

IR (Nujol) : 1615, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 2.76 (3H, s), 2.96 (2H, t, J=8 Hz), 3.34 (2H, t, J=8 Hz), 6.57 (1H, d, J=9 Hz), 7.7-7.8 (2H, m), 7.94 (2H, d, J=6 Hz), 8.00 (1H, s), 8.72 (2H, d, J=6 Hz)

Mass (m/z) : 294 $(M+1)^+$

Example 64

A mixture of 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.46 g) and sodium hydride (60 %, 0.12 g) in tetrahydrofuran (10 ml) was stirred at 5℃ for 2 hours. To the resultant mixture was added 1-fluoro-2,4,6-trimethylpyridinium triflate (0.87 g). The mixture was stirred at 5℃ for 2 hours and then at room temperature for 2 hours, and poured into a mixture of ethyl acetate and water. The organic layer was

separated, dried, and evaporated. The residue was chromatographed [a mixture of hexane and ethyl acetate (1:4)] over silica gel to give 1-methyl-3-fluoro-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (97 mg) as a brown powder.

mp : 200°C

IR (KBr) : 1739, 1639, 1626 cm^{-1}

NMR (DMSO-d_6, δ) : 3.18 (3H, s), 6.07 (1H, d, J=50 Hz), 7.20 (1H, d, J=8 Hz), 7.99 (2H, d, J=6 Hz), 8.1-8.3 (2H, m), 8.36 (1H, s), 8.74 (2H, d, J=6 Hz)

Mass (m/z) : 326 $(M+1)^+$

Example 65

A mixture of 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.21 g), potassium hydroxide (27 mg) and benzaldehyde (0.07 ml) in ethanol (5.3 ml) was stirred at room temperature for 2 hours. The resultant precipitates were collected and purified by chromatography (methylene chloride) over silica gel to give 1-methyl-3-benzylidene-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.21 g) as a brown powder.

mp : 230°C

IR (KBr) : 1705 cm^{-1}

NMR (DMSO-d_6, δ) : 3.28 (3H, s), 7.1-7.2 (1H, m), 7.4-8.2 (9H, m), 8.2-8.6 (2H, m), 8.7-8.9 (2H, m)

Mass (m/z) : 396 $(M+1)^+$

Example 66

A mixture of 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.35 g) and tert-butoxybis(dimethylamino)methane (0.24 g) in N,N-dimethylformamide (2 ml) was stirred at room temperature for 1 hour, and then poured into water. The resultant precipitates were collected and washed successively with water and ethyl acetate to give 1-methyl-

3-(dimethylamino)methylidene-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.38 g) as a gray powder.

mp : 260℃

IR (KBr) : 1668, 1593 cm^{-1}

Mass (m/z) : 363 $(M+1)^+$

Example 67

A mixture of 1-methyl-3-(dimethylamino)methylidene-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.16 g) and hydrochloric acid (1N, 0.88 ml) in tetrahydrofuran (3 ml) was stirred at 50℃ for 2 hours. The resultant precipitates were collected and suspended in a mixture of methylene chloride and water. The reaction suspension was adjusted to pH 4, and the resultant precipitates were collected and washed successively with water and methylene chloride to give 1-methyl-3-(hydroxymethylidene)-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.11 g) as a yellow powder.

mp : 220℃ (dec.)

IR (KBr) : 3435, 1693, 1647, 1624 cm^{-1}

NMR (DMSO-d_6, δ) : 3.21 (3H, s), 7.07 (1H, d, J=8 Hz), 7.8-8.0 (4H, m), 8.19 (1H, s), 8.24 (1H, d, J=2 Hz), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 336 $(M+1)^+$

Example 68

A mixture of 1-methyl-3-(dimethylamino)methylidene-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.18 g) and sodium periodate (0.64 g) in tetrahydrofuran (2 ml) and water (2 ml) was stirred at room temperature overnight. To the resultant mixture was added ethyl acetate and the insoluble material was filtered off. The filtrate was separated, and the organic layer was washed with aqueous sodium bicarbonate, dried, and evaporated. The residue was chromatographed [a mixture of hexane

and ethyl acetate (1:4)] over silica gel to give 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]isatin (74 mg) as a red-brown powder.

mp : 235°C

IR (KBr) : 1739, 1624 cm^{-1}

NMR (DMSO-d_6, δ) : 3.20 (3H, s), 7.28 (1H, d, J=8 Hz), 7.98 (2H, d, J=6 Hz), 8.21 (1H, d, J=2 Hz), 8.39 (1H, dd, J=8, 2 Hz), 8.44 (1H, s), 8.74 (2H, d, J=6 Hz)

Mass (m/z) : 322 $(M+1)^+$

Example 69

A mixture of 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]isatin (0.11 g) and sodium borohydride (13 mg) in methanol (5 ml) was acidified to pH 3 with hydrochloric acid, and then stirred for 1 hour at room temperature. The resultant insoluble material was filtered off, and to the filtrate were added ethyl acetate and water. The reaction mixture was alkalified, and the organic layer was dried and evaporated. The residue was chromatographed [a mixture of ethyl acetate and methanol (10:1)] over silica gel to give 1-methyl-3-hydroxy-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (92 mg) as a white powder.

mp : 210°C (dec.)

IR (KBr) : 3424, 1711, 1626, 1512, 1479 cm^{-1}

NMR (DMSO-d_6, δ) : 3.14 (3H, s), 5.02 (1H, d, J=8 Hz), 6.38 (1H, d, J=8 Hz), 7.10 (1H, d, J=9 Hz), 7.98 (2H, d, J=6 Hz), 8.0-8.1 (2H, m), 8.30 (1H, s), 8.74 (2H, d, J=6 Hz)

Mass (m/z) : 324 $(M+1)^+$

Example 70

A mixture of 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]isatin (0.13 g) and diethylamino sulfur trifluoride (0.16 ml) in methylene chloride (1.3 ml) was stirred at room temperature for 2 days. To the resultant

mixture were added methylene chloride and water, and then neutralized to pH 7. The organic layer was dried and evaporated, and the residue was chromatographed [a mixture of hexane and ethyl acetate (1:3)] over silica gel to give 1-methyl-3,3-difluoro-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (57 mg) as a pale brown powder.

mp : 175°C

IR (KBr) : 1747, 1639, 1514 cm^{-1}

NMR (DMSO-d_6, δ) : 3.24 (3H, s), 7.37 (1H, d, J=8 Hz), 8.01 (2H, d, J=6 Hz), 8.3-8.5 (2H, m), 8.46 (1H, s), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 344 $(M+1)^+$

Example 71

A mixture of 1-methyl-5-[2-(4-pyridyl)thiazol-4-yl]isatin (0.13 g), methoxylamine hydrochloride (37 mg) and sodium acetate (37 mg) in methanol (2 ml) was refluxed for 1.5 hours. To the resultant mixture were added ethyl acetate and water, and then alkalified to pH 9. The organic layer was separated, dried and evaporated. The residue was washed with a mixture of ethyl acetate and diisopropyl ether to give 1-methyl-3-methoxyimino-5-[2-(4-pyridyl)thiazol-4-yl]oxindole (0.11 g) as a brown powder.

mp : 160°C

IR (KBr) : 1709, 1647, 1622 cm^{-1}

NMR (DMSO-d_6, δ) : 3.21 (3H, s), 4.29 (3H, s), 7.21 (1H, d, J=8 Hz), 7.96 (2H, d, J=6 Hz), 8.18 (1H, dd, J=8, 2 Hz), 8.32 (1H, s), 8.51 (1H, d, J=2 Hz), 8.74 (2H, d, J=6 Hz)

Mass (m/z) : 351 $(M+1)^+$

Example 72

The following compound was obtained in a similar manner to that of Example 6-(1).

1-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 100℃

IR (KBr) : 1641, 1604, 1485 cm^{-1}

NMR (DMSO-d_6, δ) : 2.0-2.2 (4H, m), 2.6-2.8 (2H, m), 3.28 (3H, s), 7.3-7.5 (1H, m), 7.8-8.5 (5H, m), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 336 $(M+1)^+$

Example 73

The following compound was obtained in a similar manner to that of Example 6-(1).

1-ethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 110℃

IR (KBr) : 1655, 1603 cm^{-1}

NMR (DMSO-d_6, δ) : 1.05 (3H, t, J=7 Hz), 2.0-2.3 (4H, m), 2.7-2.9 (2H, m), 3.85 (2H, broad), 7.46 (1H, d, J=9 Hz), 7.9-8.1 (4H, m), 8.36 (1H, s), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 350 $(M+1)^+$

Example 74

The following compound was obtained in a similar manner to that of Example 6-(1).

1-(carbamoylmethyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 240℃

IR (KBr) : 3413, 1707, 1641 cm^{-1}

NMR (DMSO-d_6, δ) : 2.0-2.4 (4H, m), 2.8-3.1 (2H, m), 4.34 (2H, s), 7.05 (1H, s), 7.36 (1H, d, J=9 Hz), 7.50 (1H, s), 7.9-8.0 (4H, m), 8.34 (1H, s), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 379 $(M+1)^+$

Example 75

The following compound was obtained in a similar manner to that of Example 6-(1).

1-butyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp : 230°C

IR (KBr) : 3400, 1639, 1631, 1512 cm^{-1}

NMR (DMSO-d_6, δ) : 0.83 (3H, t, J=7 Hz), 1.1-1.5 (4H, m), 2.0-2.3 (4H, m), 2.7-2.9 (2H, m), 3.7-4.1 (2H, broad), 7.50 (1H, d, J=9 Hz), 8.0-8.1 (2H, m), 8.53 (2H, d, J=6 Hz), 8.62 (1H, s), 9.00 (2H, d, J=6 Hz)

Mass (m/z) : 378 $(M+1)^+$

Example 76

The following compound was obtained in a similar manner to that of Example 6-(1).

1-(2,2-difluoroethyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp : 240°C

IR (KBr) : 3430, 1658, 1648, 1512 cm^{-1}

NMR (DMSO-d_6, δ) : 2.0-2.4 (4H, m), 2.7-2.9 (2H, m), 4.0-5.0 (2H, m), 6.24 (1H, tt, J=56, 4 Hz), 7.55 (1H, d, J=9 Hz), 8.0-8.1 (2H, m), 8.48 (2H, d, J=6 Hz), 8.61 (1H, s), 8.98 (2H, d, J=6 Hz)

Mass (m/z) : 386 $(M+1)^+$

Example 77

The following compound was obtained in a similar manner to that of Example 6-(1).

1-benzyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp : 250℃

IR (KBr) : 3400, 1647, 1512 cm^{-1}

NMR (DMSO-d_6, δ) : 2.0-2.4 (4H, m), 2.5-2.7 (2H, m), 5.08 (2H, s), 7.2-7.4 (5H, m), 7.52 (1H, d, J=8 Hz), 7.9-8.1 (2H, m), 8.43 (2H, d, J=6 Hz), 8.53 (1H, s), 8.95 (2H, d, J=6 Hz)

Mass (m/z) : 412 $(M+1)^+$

Preparation 19

The following compound was obtained in a similar manner to that of Preparation 1.

8-(chloroacetyl)-3,4,5,6-tetrahydro-1H-1-benzo[b]azocin-2-one

IR (KBr) : 3178, 3072, 2937, 1705, 1658, 1568 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-3.0 (8H, m), 5.17 (2H, s), 7.51 (1H, d, J=8 Hz), 7.61 (1H, d, J=2 Hz), 7.85 (1H, dd, J=8, 2 Hz), 9.70 (1H, s)

Mass (m/z) : 252 $(M+1)^+$

Example 78

The following compound was obtained in a similar manner to that of Example 1.

8-[2-(4-pyridyl)thiazol-4-yl]-3,4,5,6-tetrahydro-1H-1-benzo[b]azocin-2-one

mp : 245°C

IR (KBr) : 3430, 1658, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.4-3.0 (8H, m), 7.44 (1H, d, J=8 Hz), 7.76 (1H, d, J=2 Hz), 7.92 (1H, dd, J=8, 2 Hz), 7.97 (2H, d, J=6 Hz), 8.36 (1H, s), 8.75 (2H, d, J=6 Hz), 9.63 (1H, s)

Mass (m/z) : 336 $(M+1)^+$

Example 79

The following compound was obtained in a similar manner to that of Example 6-(1).

1-methyl-8-[2-(4-pyridyl)thiazol-4-yl]-3,4,5,6-tetrahydro-1H-1-benzo[b]azocin-2-one

mp : 175°C

IR (KBr) : 1637 cm^{-1}

NMR (DMSO-d_6, δ) : 1.2-1.8 (2H, m), 1.8-2.4 (5H, m), 2.7-2.9 (1H, m), 3.28 (3H, s), 7.47 (1H, d, J=8 Hz), 7.9-8.1 (4H, m), 8.42 (1H, s), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 350 $(M+1)^+$

Example 80

The following compound was obtained in a similar manner to that of Example 1-(1).

1-methyl-8-[2-(4-pyridyl)thiazol-4-yl]-1,2,3,4,5,6-hexahydro-benzo[b]azocine dihydrochloride

mp : 265°C

IR (KBr) : 3404, 2548, 1630, 1512 cm^{-1}

NMR (DMSO-d_6, δ) : 1.2-4.0 (10H, m), 3.43 (3H, s), 7.51 (1H, d, J=8 Hz), 8.17 (1H, d, J=8 Hz), 8.3-8.5 (3H, m), 8.72 (1H, s), 8.93 (2H, d,

J=6 Hz)

Mass (m/z) : 336 $(M+1)^+$

Example 81

The following compound was obtained in a similar manner to that of Example 6-(1).

1-ethyl-8-[2-(4-pyridyl)thiazol-4-yl]-3,4,5,6-tetrahydro-1H-benzo[b]azocin-2-one

mp : 180°C

IR (KBr) : 1639 cm^{-1}

NMR (DMSO-d_6, δ) : 1.01 (3H, t, J=7 Hz), 1.2-2.4 (7H, m), 2.8-3.0 (1H, m), 3.3-3.6 (1H, m), 4.2-4.4 (1H, m), 7.47 (1H, d, J=9 Hz), 7.9-8.1 (4H, m), 8.43 (1H, s), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 364 $(M+1)^+$

Example 82

A mixture of 1-isopropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (0.3 g) and phosphorus pentasulfide (0.37 g) in dioxane (5 ml) was stirred at 90°C overnight. To the resultant mixture were added methylene chloride and 4N aqueous sodium hydroxide (3 ml), and then the organic layer was separated, dried, and evaporated. The residue was chromatographed [a mixture of methylene chloride and ethyl acetate (1:1)] over slica gel to give 1-isopropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-thione (0.21 g) as a pale brown powder.

mp : 216-219°C

IR (KBr) : 1597, 1481 cm^{-1}

NMR ($CDCl_3$, δ) : 1.01 (3H, d, J=7 Hz), 1.58 (3H, d, J=7 Hz), 1.8-3.2 (6H, m), 5.8-6.0 (1H, m), 7.31 (1H, d, J=8 Hz), 7.69 (1H, s), 7.8-8.4 (4H, m), 8.76 (2H, broad)

Mass (m/z) : 380 $(M+1)^+$

Example 83

The following compound was obtained in a similar manner to that of Example 6-(1).

1-(sec-butyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 138-139℃

NMR ($CDCl_3$, δ) : 0.7-2.0 (8H, m), 1.8-2.5 (4H, m), 2.6-3.0 (2H, m), 4.4-4.7 (1H, m), 7.24 (1H, d, J=7 Hz), 7.65 (1H, s), 7.8-7.9 (2H, m), 7.99 (2H, d, J=6 Hz), 8.75 (2H, broad)

Mass (m/z) : 378 $(M+1)^+$

Example 84

The following compound was obtained in a similar manner to that of Example 6-(1).

1-neopentyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 190-191℃

NMR ($CDCl_3$, δ) : 0.85 (9H, s), 1.9-2.4 (4H, m), 2.7-3.3 (3H, m), 4.4-4.6 (1H, m), 7.33 (1H, d, J=9 Hz), 7.62 (1H, s), 7.8-8.0 (4H, m), 8.75 (2H, broad)

Mass (m/z) : 392 $(M+1)^+$

Example 85

The following compound was obtained in a similar manner to that of Example 6-(1).

1-(1-ethylpropyl)-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 0.81 (3H, t, J=7 Hz), 1.02 (3H, t, J=7 Hz), 1.5-2.5 (8H, m), 2.6-3.1 (2H, m), 4.2-4.5 (1H, m), 7.24 (1H, d, J=8 Hz), 7.65 (1H, s), 7.8-7.9 (2H, m), 7.99 (2H, d, J=5 Hz), 8.75 (2H, broad)

Mass (m/z) : 392 $(M+1)^+$

Example 86

The following compound was obtained in a similar manner to that of Example 6-(1).

1-cyclopentyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp : 225-228℃

NMR ($CDCl_3$, δ) : 1.4-2.5 (12H, m), 2.6-3.0 (2H, m), 4.6-4.8 (1H, m), 7.29 (1H, d, J=10 Hz), 7.8-7.9 (2H, m), 7.90 (1H, s), 8.51 (2H, broad), 8.88 (2H, broad)

MS (m/z) : 390 $(M+1)^+$

Example 87

The following compound was obtained in a similar manner to that of Example 6-(1).

1-cyclohexyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

mp : 215-220℃

NMR (DMSO-d_6, δ) : 1.2-2.3 (14H, m), 2.7-2.9 (2H, m), 4.1-4.4 (1H, m), 7.40 (1H, d, J=9 Hz), 7.9-8.1 (2H, m), 8.32 (2H, d, J=6 Hz), 8.52 (1H, s), 8.90 (2H, d, J=6 Hz)

Mass (m/z) : 404 $(M+1)^+$

Example 88

The following compound was obtained in a similar manner to that of Example 6-(1).

1-cycloheptyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

NMR (DMSO-d_6, δ) : 1.4-2.3 (16H, m), 2.7-2.8 (2H, m), 4.2-4.4 (1H, m), 7.38 (1H, d, J=9 Hz), 8.0-8.1 (2H, m), 8.54 (2H, d, J=7 Hz), 8.62 (1H, s), 9.02 (2H, d, J=7 Hz)

Mass (m/z) : 418 $(M+1)^+$

Example 89

The following compound was obtained in a similar manner to that of Example 43.

4-[4-(1-isopropyl-1,3,4,5-tetrahydro-2-oxo-2H-1-benzazepin-7-yl)thiazol-2-yl]pyridine 1-oxide

mp : 239-240°C

IR (KBr) : 1647, 1604 cm^{-1}

NMR (DMSO-d_6, δ) : 1.0-1.1 (3H, m), 1.3-1.5 (3H, m), 1.8-2.2 (4H, m), 2.7-2.8 (2H, m), 4.5-4.7 (1H, m), 7.36 (1H, d, J=9 Hz), 7.9-8.1 (4H, m), 8.3-8.4 (3H, m)

Mass (m/z) : 380 $(M+1)^+$

Example 90

A solution of 4-[4-(1-isopropyl-1,3,4,5-tetrahydro-2-oxo-2H-1-benzazepn-7-yl)thiazol-2-yl]pyridine 1-oxide (0.5 g) in acetic anhydride (10 ml) was refluxed overnight. The solvent was evaporated, and to the residue were added 4N aqueous sodium hydroxide (20 ml) and methylene

chloride. The whole mixture was stirred at room temperature for 3 hours and then acidified with hydrochloric acid. The resultant organic layer was separated, dried, and evaporated. The residue was chromatographed [a mixture of methylene chloride and methanol (50:1)] over slica gel and the desired product was recrystallized from ethanol to give 1-isopropyl-7-[2-(2-pyridon-4-yl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (0.22 g) as pale brown crystals.

mp : > 260℃

IR (KBr) : 1654, 1644, 1621, 1529, 1475 cm^{-1}

NMR (DMSO-d_6, δ) : 1.0-1.2 (3H, m), 1.3-1.5 (3H, m), 1.8-2.3 (4H, m), 2.7-2.8 (2H, m), 4.5-4.7 (1H, m), 6.7-7.0 (2H, m), 7.3-7.6 (2H, m), 7.9-8.4 (3H, m), 11.83 (1H, s)

Mass (m/z) : 380 $(M+1)^+$

Example 91

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-7-[2-(1-methyl-2-pyridon-4-yl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 179-180℃

IR (KBr) : 1666, 1641, 1599, 1531, 1467 cm^{-1}

NMR ($CDCl_3$, δ) : 1.10 (3H, d, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.8-2.5 (4H, m), 2.6-2.9 (2H, m), 3.61 (3H, s), 4.7-5.0 (1H, m), 6.95 (1H, dd, J=7, 2 Hz), 7.1-7.5 (3H, m), 7.61 (1H, s), 7.8-7.9 (2H, m)

Mass (m/z) : 394 $(M+1)^+$

Example 92

A mixture of 4-[4-(1-isopropyl-1,3,4,5-tetrahydro-2-oxo-2H-1-benzazepin-7-yl)thiazol-2-yl]pyridine 1-oxide (0.30 g), trimethylsilyl

cyanide (0.42 ml) and triethylamine (0.22 ml) in acetonitrile (3 ml) was refluxed overnight. To the resultant mixture were added ethyl acetate and water, and then the organic layer was separated, dried and evaporated. The residue was chromatographed [a mixture of methylene chloride and ethyl acetate (1:1)] over slica gel and the product was crystallized from a mixture of ethanol and diisopropyl ether to give 1-isopropyl-7-[2-(2-cyano-4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (0.22 g) as pale brown crystals.

mp : 146-149℃

IR (KBr) : 2241, 1645, 1595 cm^{-1}

NMR ($CDCl_3$, δ) : 1.12 (3H, d, J=7 Hz), 1.49 (3H, d, J=7 Hz), 1.9-2.5 (4H, m), 2.6-3.0 (2H, m), 4.7-5.0 (1H, m), 7.31 (1H, d, J=9 Hz), 7.70 (1H, s), 7.8-8.1 (3H, m), 8.36 (1H, d, J=1 Hz), 8.83 (1H, d, J=5 Hz)

Mass (m/z) : 389 $(M+1)^+$

Example 93

A mixture of 1-isopropyl-7-[2-(2-cyano-4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (0.10 g) and 4N hydrogen chloride in dioxane (2 ml) in ethanol (2 ml) was refluxed for 1 hour and then evaporated. To the residue were added methylene chloride and water, and then the organic layer was separated, dried, and evaporated. The residue was crystallized from a mixture of ethanol and diisopropyl ether to give 1-isopropyl-7-[2-(2-ethoxycarbonyl-4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (90 mg) as a pale brown powder.

mp : 150-170℃

IR (KBr) : 1718, 1695, 1643, 1599 cm^{-1}

NMR ($CDCl_3$, δ) : 1.11 (3H, d, J=7 Hz), 1.4-1.6 (6H, m), 1.9-2.5 (4H, m), 2.6-3.0 (2H, m), 4.4-5.0 (3H, m), 7.30 (1H, d, J=9 Hz), 7.6-8.2 (4H, m), 8.7-8.8 (2H, m)

Mass (m/z) : 436 $(M+1)^+$

Example 94

The following compound was obtained in a similar manner to that of Example 1.

1-isopropyl-7-[2-(2-methyl-5-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.10 (3H, d, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.8-2.4 (4H, m), 2.69 (3H, s), 2.6-3.0 (2H, m), 4.7-5.0 (1H, m), 7.2-7.4 (2H, m), 7.55 (1H, s), 7.8-7.9 (2H, m), 8.31 (1H, dd, J=8, 2 Hz), 9.14 (1H, d, J=2 Hz)

Mass (m/z) : 378 $(M+1)^+$

Example 95

The following compound was obtained in a similar manner to that of Example 1.

1-isopropyl-7-[2-(3-pyridylmethyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.08 (3H, d, J=7 Hz), 1.46 (3H, d, J=7 Hz), 1.8-2.4 (4H, m), 2.6-2.9 (2H, m), 4.45 (2H, s), 4.7-5.0 (1H, m), 7.2-7.5 (2H, m), 7.40 (1H, s), 7.7-7.9 (3H, m), 8.5-8.9 (2H, m)

Mass (m/z) : 378 $(M+1)^+$

Example 96

The following compound was obtained in a similar manner to that of Example 1.

1-isopropyl-7-[2-(4-pyrimidinyl)thiazol-4-yl]-1,3,4,5-tetrahydro-

2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.11 (3H, d, J=7 Hz), 1.49 (3H, d, J=7 Hz), 1.9-2.5 (4H, m), 2.6-3.0 (2H, m), 4.7-5.0 (1H, m), 7.30 (1H, d, J=9 Hz), 7.77 (1H, s), 7.8-7.9 (2H, m), 8.30 (1H, d, J=5 Hz), 8.9-9.0 (1H, m), 9.27 (1H, s)

Mass (m/z) : 365 $(M+1)^+$

Preparation 20

The following compound was obtained in a similar manner to that of Preparation 18.

3-methylpyridine-4-thiocarboxamide

NMR (DMSO-d_6, δ) : 2.28 (3H, s), 7.16 (1H, d, J=5 Hz), 8.39 (1H, d, J=5 Hz), 8.43 (1H, s), 9.69 (1H, s), 10.21 (1H, s)

Mass (m/z) : 153 $(M+1)^+$

Example 97

The following compound was obtained in a similar manner to that of Example 1.

1-isopropyl-7-[2-(3-methyl-4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

NMR (DMSO-d_6, δ) : 1.09 (3H, d, J=7 Hz), 1.39 (3H, d, J=7 Hz), 1.8-2.3 (4H, m), 2.7-2.9 (2H, m), 2.80 (3H, s), 4.5-4.8 (1H, m), 7.39 (1H, d, J=9 Hz), 7.9-8.1 (2H, m), 8.38 (1H, d, J=6 Hz), 8.61 (1H, s), 8.79 (1H, d, J=6 Hz), 8.92 (1H, s)

Mass (m/z) : 378 $(M+1)^+$

Example 98

The following compounds was obtained in a similar manner to

that of Example 10.

1-(4-pyridylmethyl)-5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.44 (6H, s), 2.18 (2H, t, J=7 Hz), 2.50 (2H, t, J=7 Hz), 4.95 (2H, broad), 7.05 (1H, d, J=8 Hz), 7.28 (2H, d, J=6 Hz), 7.60 (1H, s), 7.7-8.1 (4H, m), 8.62 (2H, d, J=6 Hz), 8.74 (2H, d, J=6 Hz)

Mass (m/z) : 441 $(M+1)^+$

Example 99

The following compound was obtained in a similar manner to that of Example 1.

5,5-dimethyl-7-[2-(2-chloro-4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR (DMSO-d_6, δ) : 1.42 (6H, s), 2.04 (2H, t, J=7 Hz), 2.25 (2H, t, J=7 Hz), 7.08 (1H, d, J=8 Hz), 7.8-8.1 (4H, m), 8.39 (1H, S), 8.57 (1H, d, J=5 Hz), 9.67 (1H, s)

Mass (m/z) : 384 $(M+1)^+$

Example 100

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-5,5-dimethyl-7-[2-(2-chloro-4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.03 (3H, d, J=7 Hz), 1.35 (3H, s), 1.5-1.6 (6H, m), 1.8-2.4 (4H, m), 4.6-4.9 (1H, m), 7.27 (1H, d, J=8 Hz), 7.66 (1H, s), 7.8-8.1 (4H, m), 8.51 (1H, d, J=5 Hz)

Mass (m/z) : 426 $(M+1)^+$

Example 101

The following compound was obtained in a similar manner to that of Example 54.

1-isopropyl-5,5-dimethyl-7-[2-(2-methoxy-4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.03 (3H, d, J=7 Hz), 1.34 (3H, s), 1.5-1.6 (6H, m), 1.8-2.4 (4H, m), 4.01 (3H, s), 4.6-4.9 (1H, m), 7.2-7.6 (3H, m), 7.59 (1H, s), 7.8-8.1 (2H, m), 8.28 (1H, d, J=5 Hz)

Mass (m/z) : 422 $(M+1)^+$

Example 102

A mixture of 1-isopropyl-5,5-dimethyl-7-[2-(2-chloro-4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (0.3 g), cyclopropylamine (1 ml), dioxane (5 ml) and water (0.5 ml) was heated at 220℃ for 10 hours in a steel bomb. To the resultant mixture were added ethyl acetate and water, and then the organic layer was separeted, washed with water, dried and evaporated. The residual oil was chromatographed [a mixture of toluene and ethyl acetate (2:1)] over silica gel, and the product was crystallized from diisopropyl ether to give 1-isopropyl-5,5-dimethyl-7-[2-(2-cyclopropylamino-4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (45 mg) as a pale brown powder.

NMR ($CDCl_3$, δ) : 0.6-0.7 (2H, m), 0.8-1.0 (2H, m), 1.03 (3H, d, J=7 Hz), 1.34 (3H, s), 1.5-1.6 (6H, m), 1.8-2.4 (4H, m), 2.6-2.7 (1H, m), 4.6-4.9 (1H, m), 5.19 (1H, s), 7.2-7.4 (3H, m), 7.58 (1H, s), 7.86 (1H, dd, J=8, 2 Hz), 8.08 (1H, d, J=2 Hz), 8.18 (1H, d, J=5 Hz)

Mass (m/z) : 447 $(M+1)^+$

Example 103

The following compound was obtained in a similar manner to that of Example 102.

1-isopropyl-5,5-dimethyl-7-{2-[2-(1-imidazolyl)-4-pyridyl]thiazol-4-yl}-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.04 (3H, d, J=7 Hz), 1.36 (3H, s), 1.5-1.6 (6H, m), 1.8-2.4 (4H, m), 4.6-4.9 (1H, m), 7.2-7.4 (2H, m), 7.68 (1H, s), 7.7-8.1 (5H, m), 8.46 (1H, s), 8.60 (1H, d, J=5 Hz)

Mass (m/z) : 458 $(M+1)^+$

Example 104

The following compound was obtained in a similar manner to that of Example 1.

5,5-dimethyl-7-[2-(3-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.51 (6H, s), 2.17 (2H, t, J=7 Hz), 2.46 (2H, t, J=7 Hz), 7.03 (1H, d, J=8 Hz), 7.3-7.5 (1H, m), 7.53 (1H, s), 7.7-8.4 (4H, m), 8.6-8.8 (1H, m), 9.2-9.3 (1H, m)

Mass (m/z) : 350 $(M+1)^+$

Example 105

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-5,5-dimethyl-7-[2-(3-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one hydrochloride

NMR (DMSO-d_6, δ) : 0.97 (3H, d, J=7 Hz), 1.26 (3H, s), 1.4-1.6 (6H, m), 1.8-2.3 (4H, m), 4.5-4.7 (1H, m), 7.34 (1H, d, J=8 Hz), 7.7-8.1

(3H, m), 8.38 (1H, s), 8.5-8.9 (2H, m), 9.3-9.4 (1H, m)

Mass (m/z) : 392 $(M+1)^+$

Example 106

The following compound was obtained in a similar manner to that of Example 43.

3-[4-(1-isopropyl-1,3,4,5-tetrahydro-2-oxo-2H-1-benzazepin-7-yl)thiazol-2-yl]pyridine 1-oxide

NMR ($CDCl_3$, δ) : 1.03 (3H, d, J=7 Hz), 1.34 (3H, s), 1.5-1.6 (6H, m), 1.8-2.4 (4H, m),4.6-4.9 (1H, m), 7.2-7.5 (2H, m), 7.63 (1H, s), 7.7-8.3 (4H, m), 8.97 (1H, s)

Mass (m/z) : 408 $(M+1)^+$

Preparation 21-1

A solution of sodium hydride (60 % suspension in mineral oil, 18.8 g, 0.470 mol) in tetrahydrofuran (450 ml) was stirred at room temperature. To the above solution was added a solution of phenyl acetic acid ethyl ester (25.7 g, 0.157 mol) in tetrahydrofuran (100 ml) dropwise over 1 hour, and the whole mixture was stirred under the same conditions for 1 hour. To the resultant mixture was added ethyl iodide (30.1 ml, 0.377 mol) under ice bath cooling. The reaction mixture was stirred at room temperature for 3 days, and then added 6 N-hydrochloric acid to justify pH 6. The solvent (tetrahydrofuran) was removed in vacuo to give an oily residue, which was extracted with ethyl acetate. The resultant extract was washed with brine, and dried over magnesium sulfate. The solvent was removed in vacuo to afford an oily residue, which was subjected to column chromatography over silica gel eluting with a mixture of ethyl acetate and n-hexane to give 2-ethyl-2-phenylbutyric acid ethyl ester (26.85 g, 77.6 %) as a colorless oil.

IR : 1729 cm^{-1}

NMR ($CDCl_3$) : 0.73 (6H, t, J=7.4 Hz), 1.17 (3H, t, J=7.1 Hz), 1.9-2.2 (4H, m), 4.12 (2H, q, J=7.1 Hz), 7.15-7.35 (5H, m)

Mass (APCI, m/z) : 221 (M+1)

Preparation 21-2

A suspension of lithium aluminum hydride (3.08 g, 81.1 mmol) in tetrahydrofuran (100 ml) was stirred under ice bath cooling. To the reaction suspension was added a solution of 2-ethyl-2-phenylbutyric acid ethyl ester (26.8 g, 0.122 mol) in tetrahydrofuran (25 ml) under the same conditions. After 1 hour, to the resulting mixture were added sodium fluoride (13.62 g, 0.324 mol) and then water (4.4 ml) slowly. The whole mixture was stirred at room temperature for 1 hour and filtered to remove pale gray precipitates. The resultant filtrate was evaporated in vacuo to give 2-ethyl-2-phenylbutanol (20.89 g, 96.0 %) as a colorless oil.

NMR ($CDCl_3$) : 0.75 (6H, t, J=7.4 Hz), 1.11 (1H, t, J=6.3 Hz), 1.6-2.1 (4H, m), 3.74 (2H, d, J=6.3 Hz), 7.15-7.40 (5H, m)

Preparation 21-3

A solution of oxalyl chloride (11.2 ml, 0.128 mol) in methylene chloride (285 ml) was stirred under -70°C. To the reaction solution was added dimethylsulfoxide (9.1 ml, 0.128 mol) in methylene chloride (58 ml), and then whole mixture was stirred under the same conditions for 5 minutes. To the reaction mixture was added 2-ethyl-2-phenylbutanol (20.8 g, 0.117 mol) in methylene chloride (110 ml), and then stirred under the same conditions for 15 minutes. Then to the resulting mixture was added triethylamine (81.5 ml), and the whole mixture was stirred for 30 minutes. As a result, the temperature of the reaction mixture was allowed to rise to room temperature gradually. To the

reaction mixture was added water (250 ml) and extracted with methylene chloride. The resulting extract was dried over magnesium sulfate. The solvent was removed in vacuo to give an oily residue, which was subjected to column chromatography over silica gel eluting with a mixture of ethyl acetate and n-hexane to afford 2-ethyl-2-phenylbutanal (18.46 g, 89.5 %) as a pale yellow oil.

NMR ($CDCl_3$) : 0.76 (6H, t, J=7.5 Hz), 1.97 (4H, q, J=7.5 Hz), 7.18-7.42 (5H, m), 9.49 (1H, s)

Mass (APCI, m/z) : 177 (M+1)

Preparation 21-4

A suspension of sodium hydride (4.61 g, 0.115 mol) in tetrahydrofuran (46 ml) was stirred at 40°C. To the reaction suspension was added diethyl phosphonoacetic acid ethyl ester (22.8 ml, 0.115 mol) slowly, and the whole mixture was stirred for 5 minutes. To the reaction mixture was added 2-ethyl-2-phenylbutanal (18.46 g, 0.105 mol), and stirred under the same conditions for 15 minutes. To the resulting mixture were added water and ethyl acetate. The organic layer was separated, washed successively with water and brine, and dried. The solvent was removed in vacuo to give a pale yellow oil, which was subjected to column chromatography over silica gel eluting with a mixture of ethyl acetate and n-hexane to give 4-ethyl-4-phenyl-2-hexenoic acid ethyl ester (23.83 g, 92.4 %) as a pale yellow oil.

NMR ($CDCl_3$) : 0.73 (6H, t, J=7.4 Hz), 1.30 (3H, t, J=7.1 Hz), 1.86 (4H, q, J=7.4 Hz), 4.20 (2H, q, J=7.1 Hz), 5.86 (1H, d, J=16.1 Hz), 7.07 (1H, d, J=16.1 Hz), 7.15-7.36 (5H, m)

Mass (APCI, m/z) : 246 (M+1).

Preparation 21-5

A mixture of 4-ethyl-4-phenyl-2-hexenoic acid ethyl ester (23.8 g,

99.6 mmol) and 10 % palladium on carbon (2.38 g) in methanol (210 ml) was stirred under 3 atmospheric pressure of hydrogen at room temperature for 3 hours. The palladium on carbon was removed by filtration. The resultant filtrate was evaporated in vacuo to give a pale black oily residue, which was subjected to column chromatography over silica gel eluting with ethyl acetate. The resulting fractions containing a desired compound were combined and then evaporated in vacuo to give 4-ethyl-4-phenylhexanoic acid ethyl ester (24.0 g, 100 %) as a colorless oil.

NMR ($CDCl_3$) : 0.69 (6H, t, J=7.4 Hz), 1.21 (3H, t, J=7.2 Hz), 1.5-1.8 (4H, m), 1.90 (4H, s), 4.09 (2H, q, J=7.1 Hz), 7.1-7.36 (5H, m)

Mass (APCI, m/z) : 249 (M+1)

Preparation 21-6

A mixture of 4-ethyl-4-phenylhexanoic acid ethyl ester (24.0 g, 97.0 mmol) and 2N sodium hydroxide solution (97 ml) in methanol (97 ml) was stirred at room temperature for 3 hours. The solvent was evaporated in vacuo to give an oily residue. To the reaction mixture was added 2N-hydrochloric acid, and then extracted twice with ethyl acetate. The resulting extract was dried over magnesium sulfate, and evaporated in vacuo to give 4-ethyl-4-phenylhexanoic acid (24.0 g, 100 %) as a colorless oil.

IR (neat) : 1710 $cm1^{-1}$

NMR ($CDCl_3$) : 0.69 (6H, t, J=7 Hz), 1.69 (4H, t, J=7 Hz), 1.9-2.1 (4H, m), 7.1-7.37 (5H, m)

Mass (APCI, m/z) : 203 ($M-H_2O$)

Preparation 21-7

A mixture of phosphorus pentoxide (97.0 g) and phosphoric acid (97 ml) was stirred at 100°C for 0.5 hours. To the reaction mixture was

added 4-ethyl-4-phenylhexanoic acid (21.4 g, 97.1 mmol). The whole mixture was stirred at 100°C for 2.5 hours and poured into ice-cooling water. The resulting mixture was extracted with ethyl acetate, washed successively with saturated solution of sodium hydrogencarbonate and brine. The reaction mixture was dried over magnesium sulfate, and evaporated to give 4,4-diethyl-α-tetralone (17.22 g, 87.7 %) as a yellow oil.

IR (neat) : 1685 cm1^{-1}

NMR ($CDCl_3$) : 0.83 (6H, t, J=7.4 Hz), 1.5-2.0 (4H, m), 2.04 (2H, t, J=7 Hz), 2.71 (2H, t, J=7 Hz), 7.2-7.33 (2H, m), 7.45-7.57 (1H, m), 8.01-8.08 (1H, m)

Mass (ESI, m/z) : 203 (M+1)

Preparation 21-8

The following compound was obtained in a similar manner to that of Preparation 12.

1-hydroxyimino-4,4-diethyl-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3326, 1452 cm^{-1}

NMR ($CDCl_3$) : 0.79 (6H, t, J=7.4 Hz), 1.5-1.81 (6H, m), 2.87 (2H, t, J=7 Hz), 7.15-7.37 (3H, m), 7.87-7.91(1H, m)

Mass (APCI, m/z) : 218 (M+1)

Preparation 21-9

The following compound was obtained in a similar manner to that of Preparation 12-(1).

5,5-diethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (KBr) : 1685 cm^{-1}

NMR ($CDCl_3$) : 0.71 (6H, t, J=7.4 Hz), 1.6-1.81 (2H, m), 1.9-2.12

(4H, m) 2.39-2.46 (2H,m) 6.93-6.98 (1H, m) 7.08-7.27 (2H, m) 7.33-7.38 (1H, m), 8.38 (1H, br)

Mass (APCI, m/z) : 218 (M+1)

Preparation 21-10

The following compound was obtained in a similar manner to that of Preparation 1.

5,5-diethyl-7-chloroacetyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (KBr) : 1677 cm^{-1}

NMR ($CDCl_3$) : 0.73 (6H, t, J=7.4 Hz), 1.6-2.2 (6H, m), 2.47-2.55 (2H, m) 4.67 (2H, s) 7.07 (1H, d, J=8.3 Hz), 7.78 (1H, dd, J=8.3 Hz and 2 Hz), 8.05 (1H, d, J=2 Hz), 8.90 (1H, br)

Mass (APCI, m/z) : 294 (M+1)

Example 107

The following compound was obtained in a similar manner to that of Example 1.

5,5-diethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (KBr) : 1662 cm^{-1}

NMR ($CDCl_3$) : 0.77 (6H, t, J=7.4 Hz), 1.7-1.9 (2H, m), 2.0-2.2 (4H, m) 2.4-2.53 (2H, m), 7.04 (1H, d, J=8.2 Hz) 7.58 (1H, s), 7.6-7.82 (2H,m), 7.89-7.92 (2H, m), 8.05 (1H, m), 8.6-8.75 (2H, br)

Mass (APCI, m/z) : 378 (M+1)

Example 108

The following compound was obtained in a similar manner to that

of Example 6-(1).

1-isopropyl-5,5-diethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Analysis : (calculated/found) $C_{25}H_{29}N_{3O}S \cdot 0.3\ H_2O$

C : 70.65/70.79, H : 7.02/7.16, N : 9.89/9.58

mp : 126.6-129.0°C

IR (KBr) : 1660 cm^{-1}

Mass (APCI, m/z) : 420 (M+1)

NMR ($CDCl_3$) : 0.5-0.6 (3H, m), 0.9-1.3 (9H, m), 1.4-2.6 (8H, m), 4.6-4.8 (1H, m), 7.25-7.30 (1H, m), 7.64 (1H, s), 7.8-8.05 (4H, m), 8.76 (2H, m)

Preparation 22-1

The following compound was obtained in a similar manner to that of Preparation 21-1.

2-phenyl-2-propylpentanoic acid ethyl ester

NMR ($CDCl_3$) : 0.89 (6H, m), 0.9-1.3 (7H, m), 1.8-2.1 (4H, m), 4.11 (2H, q, J=7.1 Hz), 7.1-7.36 (5H, m)

Mass (APCI, m/z) : 249 (M+1)

Preparation 22-2

The following compound was obtained in a similar manner to that of Preparation 21-2.

2-phenyl-2-propylpentanal

IR (neat) : 3382 cm^{-1}

NMR ($CDCl_3$) : 0.88 (6H, m), 1.0-1.3 (5H, m), 1.5-1.7 (4H, m), 3.74 (2H, d, J=6.4 Hz), 7.1-7.39 (5H, m)

Mass (APCI, negative, m/z) : 205 (M-1)

Preparation 22-3

The following compound was obtained in a similar manner to that of Preparation 21-3.

2-phenyl-2-propylpentanal

NMR ($CDCl_3$) : 0.8-1.0 (6H, m), 1.0-1.3 (4H, m), 1.8-2.0 (4H, m), 7.1-7.41 (5H, m), 9.48 (1H, s)

Mass (APCI, m/z) : 205 (M+1)

Preparation 22-4

The following compound was obtained in a similar manner to that of Preparation 21-4.

4-phenyl-4-propyl-2-heptenoic acid ethyl ester

NMR ($CDCl_3$) : 0.86 (6H, t, J=7 Hz), 1.0-1.2 (4H, m), 1.30 (3H, t, J=7.1 Hz), 1.7-1.9 (4H, m), 4.20 (2H, q, J=7.1 Hz), 5.86 (1H, d, J=16.1 Hz), 7.09 (1H, d, J=16.1 Hz), 7.14-7.36 (5H, m)

Mass (APCI, m/z) : 275 (M+1)

Preparation 22-5

The following compound was obtained in a similar manner to that of Preparation 21-5.

4-phenyl-4-propylheptanoic acid ethyl ester

IR (neat) : 1735 cm^{-1}

NMR ($CDCl_3$) : 0.85 (6H, t, J=7 Hz), 1.0-1.2 (4H, m), 1.21 (3H, t, J=7.1 Hz), 1.5-1.7 (4H, m), 2.00 (4H, s), 4.06 (2H, q, J=7.1 Hz), 7.10-7.32 (5H, m)

Mass (APCI, m/z) : 277 (M+1)

Preparation 22-6

The following compound was obtained in a similar manner to that of Preparation 21-6.

4-phenyl-4-propylheptanoic acid

IR (neat) : 1712 cm^{-1}

NMR ($CDCl_3$) : 0.86 (6H, t, J=7 Hz), 1.0-1.2 (4H, m), 1.5-1.7 (4H, m), 1.9-2.1 (4H, m), 7.10-7.32 (5H, m)

Mass (ESI, m/z) : 249 (M+1)

Preparation 22-7

The following compound was obtained in a similar manner to that of Preparation 21-7.

4,4-dipropyl-α-tetralone

IR (neat) : 1685 cm^{-1}

NMR ($CDCl_3$) : 0.87 (6H, t, J=7 Hz), 1.1-1.3 (4H, m), 1.5-1.8 (4H, m), 2.05 (2H, t, J=7.1 Hz), 2.70 (2H, t, J=7.1 Hz), 7.2-7.32 (2H, m), 7.45-7.55 (1H, m), 8.01-8.07 (1H,m)

Mass (ESI, m/z) : 231 (M+1)

Preparation 22-8

The following compound was obtained in a similar manner to that of Preparation 12.

1-hydroxyimino-4,4-dipropyl-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3245, 1457 cm^{-1}

NMR ($CDCl_3$) : 0.87 (6H, t, J=7 Hz), 1.1-1.3 (4H, m), 1.4-1.7 (4H,

m), 1.78 (2H, t, J=7 Hz), 2.86 (2H, t, J=7 Hz), 7.14-7.36 (3H, m), 7.89 (1H, dd, J=7.5 Hz and 1 Hz), 9.26 (1H, br)

Mass (ESI, m/z) : 246 (M+1)

Preparation 22-9

The following compound was obtained in a similar manner to that of Preparation 12-(1).

4,4-dipropyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (neat) : 1681 cm^{-1}

NMR ($CDCl_3$) : 0.86 (6H, t, J=7 Hz), 0.9-1.3 (4H, m), 1.5-1.7 (2H, m), 1.72-2.00 (2H, m), 2.00-2.2 (2H, m), 2.35-2.46 (2H, m), 6.92 (1H, dd, J=7.4 Hz and 2 Hz), 7.07-7.25 (2H, m), 7.36 (1H, dd, J=7.5 Hz and 2 Hz), 8.12 (1H, br)

Mass (ESI, m/z) : 246 (M+1)

Preparation 22-10

The following compound was obtained in a similar manner to that of Preparation 1.

7-chloroacetyl-4,4-dipropyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (KBr) : 1683, 1599 cm^{-1}

NMR ($CDCl_3$) : 0.88 (6H, t, J=7 Hz), 1.0-1.3 (4H, m), 1.5-2.0 (4H, m), 2.02-2.16 (2H, m), 2.46-2.54 (2H, m), 4.67 (2H, s), 7.04 (1H, d, J=8.3 Hz), 7.76 (1H, dd, J=8.3 Hz and 2 Hz), 8.04 (1H, d, J=2 Hz), 8.67 (1H, br)

Mass (ESI, m/z) : 278 ($M-H_2O$)

Example 109

The following compound was obtained in a similar manner to that of Example 1.

5,5-dipropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 156.6-158.3℃

IR (KBr) : 1675 cm^{-1}

NMR ($CDCl_3$) : 0.92 (6H, t, J=7 Hz), 1.0-1.3 (4H, m), 1.6-1.8 (2H, m), 1.9-2.2 (4H, m), 2.4-2.6 (2H, m), 6.99 (1H, d, J=8.2 Hz), 7.57 (1H, s), 7.7-7.95 (2H, m), 8.04 (2H, d, J=2 Hz), 8.74 (2H, dd, J=4.5 Hz and 2 Hz)

Mass (ESI, m/z) : 406 ($M-H_2O$)

Example 110

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-5,5-dipropyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 62.1-77.9℃

IR (KBr) : 1660 cm^{-1}

NMR ($CDCl_3$) : 0.6-2.4 (24H, m), 4.6-4.8 (1H, m), 7.25 (1H, d, J=8.2 Hz), 7.62 (1H, s), 7.8-7.95 (3H, m), 8.02 (1H, d, J=2 Hz), 8.75 (2H, dd, J=4.5 Hz and 2 Hz)

Mass (APCI, m/z) : 448 (M+1)

Preparation 23-1

A mixture of 1-phenylcyclopentanecarboxylic acid (50 g, 0.263 mol) and sulfuric acid (7.5 ml) in methanol (250 ml) was refluxed with stirring for 3.5 hours. The solvent was removed in vacuo to give a oily

residue, which was dissolved in diethyl ether. The resulting organic solution was washed successively with 0.1 N sodium hydroxide aqueous, water and brine and then dried over magnesium sulfate. The solvent was removed in vacuo to give 1-phenylcyclopentanecarboxylic acid methyl ester (48.06 g, 89.5 %) as a pale yellow oil.

NMR ($CDCl_3$) : 1.6-2.0 (6H, m), 2.5-2.75 (2H, m), 3.60 (3H, s), 7.18-7.39 (5H, m)

Mass (APCI, m/z) : 205 (M+1)

Preparation 23-2

The following compound was obtained in a similar manner to that of Preparation 21-2.

1-phenylcyclopentylmethanol

IR (KBr) : 3245 cm^{-1}

NMR ($CDCl_3$) : 1.22 (1H, br), 1.68-2.06 (8H, m), 3.51 (2H, d, J=5.4 Hz), 7.16-7.38 (5H, m)

Mass (APCI, m/z) : 159 ($M-H_2O$)

Preparation 23-3

The following compound was obtained in a similar manner to that of Preparation 21-3.

1-phenylcyclopentanecarbaldehyde

NMR ($CDCl_3$) : 1.5-2.1(6H, m), 2.4-2.6 (2H, m), 7.22-7.46 (5H, m), 9.40 (1H, s)

Mass (APCI, m/z) : 175 (M+1)

Preparation 23-4

The following compound was obtained in a similar manner to that

of Preparation 21-4.

3-(1-phenylcyclopentyl)acrylic acid ethyl ester

IR (neat) : 1716 cm^{-1}

NMR ($CDCl_3$) : 1,26 (3H, t, J=7.1 Hz), 1.6-1.8 (4H, m), 1.9-2.2 (4H, m), 4.15 (2H, q, J=7.1 Hz), 5.61 (1H, d, J=15.8 Hz), 7.06 (1H, d, J=15.8 Hz), 7.16-7.36 (5H, m)

Mass (APCI, m/z) : 245 (M+1)

Preparation 23-5

The following compound was obtained in a similar manner to that of Preparation 21-5.

3-(1-phenylcyclopentyl)propionic acid ethyl ester

NMR ($CDCl_3$) : 1.18 (3H, t, J=7.1 Hz), 1.6-2.1 (12H, m), 4.02 (2H, q, J=7.1 Hz), 7.12-7.35 (5H, m)

Mass (APCI, m/z) : 247 (M+1)

Preparation 23-6

The following compound was obtained in a similar manner to that of Preparation 21-6.

3-(1-phenylcyclopentyl)propionic acid

IR (KBr) : 1699 cm^{-1}

NMR ($CDCl_3$) : 1.5-2.1 (12H, m), 7.11-7.33 (5H, m)

Mass (APCI, m/z) : 201 ($M-H_2O$)

Preparation 23-7

The following compound was obtained in a similar manner to that of Preparation 21-7.

spiro[cyclopentane-1,4'-(α-tetralone)]

IR (neat) : 1689 cm^{-1}

NMR ($CDCl_3$) : 1.7-2.1 (8H, m), 2.06 (2H, dd, J=2 Hz and 6.4 Hz), 2.71 (2H, dd, J=2 Hz and 6.4 Hz), 7.23-7.37 (2H, m), 7.47-7.55 (1H, m), 7.99-8.03 (1H, m)

Mass (APCI, m/z) : 201 (M+1)

Preparation 23-8

The following compound was obtained in a similar manner to that of Preparation 12.

1'-(hydroxyimino)spiro[cyclopentane-1,4'- (1,2,3,4-tetrahydronaphthalene)]

IR (neat) : 3222 cm^{-1}

NMR ($CDCl_3$) : 1.7-2.0 (10H, m), 2.88 (2H, t, J=6.8 Hz), 7.15-7.37 (3H, m), 7.83-7.88 (1H, m)

Mass (APCI, m/z) : 216 (M+1)

Preparation 23-9

The following compound was obtained in a similar manner to that of Preparation 12-(1).

spiro[cyclopentane-1,5'-(1,3,4,5-tetrahydro-2H-1-benzazepin-2-one)]

IR (KBr) : 1668 cm^{-1}

NMR ($CDCl_3$) : 1.5-1.8 (4H, m), 1.83-2.05 (4H, m), 2.11-2.20 (2H, m), 2.30-2.37 (2H, m), 7.01 (1H, dd, J=7.4 Hz and 2 Hz), 7.10-7.26 (2H, m), 7.37 (1H, dd, J=7.4 Hz and 2 Hz), 8.36 (1H, br)

Mass (APCI, m/z) : 216 (M+1)

Preparation 23-10

The following compound was obtained in a similar manner to that of Preparation 1.

7'-(chloroacetyl)spiro[cyclopentane-1,5'- (1,3,4,5-tetrahydro-2H-1-benzazepin-2-one)]

IR (KBr) : 1677 cm^{-1}

NMR ($CDCl_3$) : 1.5-1.8 (4H, m), 1.9-2.05 (4H, m), 2.15-2.24 (2H, m), 2.30-2.43 (2H, m), 4.68 (2H, s), 7.11 (1H, d, J=8.2 Hz), 7.82 (1H, dd, J=8.2 Hz and 2 Hz), 8.2 (1H, d, J=2 Hz), 8.91 (1H, br)

Mass (APCI, m/z) : 292 (M+1)

Example 111

The following compound was obtained in a similar manner to that of Example 1.

7'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclopentane-1,5'-(1,3,4,5-tetrahydro-2H-1-benzazepin-2-one)]

IR (KBr) : 1683 cm^{-1}

NMR ($CDCl_3$) : 1.6-1.9 (4H, m), 1.95-2.1 (4H, m), 2.17-2.26 (2H, m), 2.35-2.44 (2H, m), 7.09 (1H, d, J=8 Hz), 7.59 (1H, s), 7.81(1H, dd, J=1.9 Hz and 8 Hz), 7.91 (2H, dd, J=4.5 Hz and 1.6 Hz), 8.05 (1H, d, J=2 Hz), 8.26 (1H, s), 8.75 (2H, dd, J=4.5 Hz and 1.6 Hz)

Mass (APCI, m/z) : 376 (M+1)

Example 112

The following compound was obtained in a similar manner to that of Example 6-(1).

1'-isopropyl-7'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclopentane-1,5'-(1,3,4,5-tetrahydro-2H-1-benzazepin-2-one)]

Analysis: (calculated/found) $C_{25}H_{27}N_3OS \cdot 0.5\ H_2O$

C : 70.39/70.32, H : 6.62/6.59, N : 9.85/9.96

mp : 193.1-195.0℃

IR (KBr) : 1652 cm^{-1}

NMR ($CDCl_3$) : 1.08 (3H, d, J=7.1 Hz), 1.39 (3H, d, J=6.2 Hz), 1.5-2.1 (8H, m), 2.17-2.29 (4H, m), 4.6-4.8 (1H, m), 7.26 (1H, d, J=8.2 Hz), 7.62 (1H, s), 7.85 (1H, dd, J=2 Hz and 8.2 Hz), 7.91 (2H, dd, J=4.5 Hz and 1.6Hz), 8.01 (1H, d, J=2 Hz), 8.75 (2H, dd, J=4.5 Hz and 1.6 Hz)

Mass (APCI, m/z) :418 (M+1)

Preparation 24-1

The following compound was obtained in a similar manner to that of Preparation 23-1.

1-phenylcyclohexanecarboxylic acid methyl ester

Mass (APCI, m/z) : 219 (M+1)

NMR ($CDCl_3$) : 1.1-1.8 (8H,m), 2.4-2.6 (2H, m), 3.63 (3H, s), 7.18-7.42 (5H, m)

Preparation 24-2

The following compound was obtained in a similar manner to that of Preparation 21-2.

1-phenylcyclohexylmethanol

IR (KBr) : 3280 cm^{-1}

NMR ($CDCl_3$) : 1.08 (1H, br), 1.3-1.7 (8H, m), 2.1-2.2 (2H, m), 3.49 (2H, d, J=3.7 Hz), 7.16-7.42 (5H, m)

Mass (APCI, m/z) : 191 (M+1)

Preparation 24-3

The following compound was obtained in a similar manner to that of Preparation 21-3.

1-phenylcyclohexanecarbaldehyde

NMR ($CDCl_3$) : 1.2-2.0 (8H, m), 2.1-2.5 (2H, m), 7.05-7.48 (5H,m), 9.37 (1H, s)

Mass (APCI, m/z) : 189 (M+1)

Preparation 24-4

The following compound was obtained in a similar manner to that of Preparation 21-4.

3-(1-phenylcyclohexyl)acrylic acid ethyl ester

NMR ($CDCl_3$) : 1.26 (3H, t, J=7.1 Hz), 1.3-1.65 (6H, m), 1.8-2.2 (4H, m), 4.15 (2H,q, J=7.1 Hz), 5.62 (1H, d, J=16.0 Hz), 6.97 (1H, d, J=16.0 Hz), 7.15-7.38 (5H, m)

Mass (APCI, m/z) : 259 (M+1)

Preparation 24-5

The following compound was obtained in a similar manner to that of Preparation 21-5.

3-(1-phenylcyclohexyl)propionic acid ethyl ester

NMR ($CDCl_3$) : 1.18 (3H, t, J=7.1 Hz), 1.3-1.7 (8H, m), 1.8-2.0 (2H, m), 2.0-2.2 (2H, m), 4.01 (2H, q, J=7.1 Hz), 7.12-7.38 (5H, m)

Mass (APCI, m/z) : 261 (M+1)

Preparation 24-6

The following compound was obtained in a similar manner to that of Preparation 21-6.

3-(1-phenylcyclohexyl)propionic acid

IR (KBr) : 1699 cm^{-1}

NMR ($CDCl_3$) : 1.3-1.7 (8H, m), 1.8-2.2 (6H, m), 7.11-7.38 (5H, m)

Mass (ESI, m/z) : 255 (M+Na)

Preparation 24-7

The following compound was obtained in a similar manner to that of Preparation 21-7.

Spiro[cyclohexane-1,4'-(α-tetralone)]

IR (neat) : 1685 cm^{-1}

NMR ($CDCl_3$) : 1.2-1.9 (10H, m), 2.17 (2H, dd, J=2 Hz and 6 Hz), 2.66 (2H, dd, J=2 Hz and 6 Hz), 7.20-7.37 (2H, m), 7.48-7.60 (1H, m), 7.99-8.05 (1H, m)

Mass (ESI, m/z) : 215 (M+1)

Preparation 24-8

The following compound was obtained in a similar manner to that of Preparation 12.

1'-(hydroxyimino)spiro[cyclohexane-1,4'-(1,2,3,4-tetrahydronaphthalene)]

IR (neat) : 3243 cm^{-1}

NMR ($CDCl_3$) : 1.2-1.8 (10H, m), 1.90 (2H, t, J=6.9 Hz), 2.81 (2H,

t, J=6.9Hz), 7.15-7.52 (3H, m), 7.83-8.01 (1H, m)

Mass (APCI, m/z) : 230 (M+1)

Preparation 24-9

The following compound was obtained in a similar manner to that of Preparation 12-(1).

spiro[cyclohexane-1,5'-(1,3,4,5-tetrahydro-2H-1-benzazepin-2-one)]

IR (KBr) :1671 cm^{-1}

NMR ($CDCl_3$) : 1.2-1.7 (6H, m), 1.83-2.05 (4H, m), 2.10-2.20 (2H, m), 2.28-2.37 (2H, m), 6.9-7.0 (1H, m), 7.1-7.26 (2H, m), 7.38-7.54 (1H, m), 8.35 (1H, br)

Mass (APCI, m/z) : 230 (M+1)

Preparation 24-10

The following compound was obtained in a similar manner to that of Preparation 1.

7'-(chloroacetyl)spiro[cyclohexane-1,5'-(1,3,4,5-tetrahydro-2H-1-benzazepin-2-one)]

IR (KBr) : 1675 cm^{-1}

NMR ($CDCl_3$) : 1.3-1.7 (6H, m), 1.8-2.0 (4H, m), 2.10-2.24 (2H, m), 2.33-2.44 (2H, m), 4.69 (2H, s), 7.08 (1H, d, J=8.2 Hz), 7.80 (1H, dd, J=8.2 Hz and 2 Hz), 8.13 (1H, d, J=2 Hz), 8.83 (1H, br)

Mass (APCI, m/z) : 306 (M+1)

Example 113

The following compound was obtained in a similar manner to that of Example 1.

7'-[2-(4-Pyridyl)thiazol-4-yl]spiro[cyclohexane-1,5'-(1,3,4,5-tetrahydro-2H-1-benzazepin-2-one)]

IR (KBr) : 1674 cm^{-1}

NMR ($CDCl_3$) : 1.2-1.7 (6H, m), 1.8-2.1 (4H, m), 2.15-2.26 (2H, m), 2.35-2.40 (2H, m), 7.06 (1H, d, J=8 Hz), 7.59 (1H, s), 7.80 (1H, dd, J=2 Hz and 8 Hz), 7.90 (2H, dd, J=4.5 Hz and 1.6 Hz), 8.14 (1H, d, J=2 Hz), 8.23 (1H, s), 8.74 (2H, dd, J=4.5 Hz and 1.6 Hz)

Mass (APCI, m/z) : 390 (M+1)

Example 114

The following compound was obtained in a similar manner to that of Example 6-(1).

1'-isopropyl-7'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclohexane-1,5'-(1,3,4,5-tetrahydro-2H-1-benzazepin-2-one)]

Analysis: (calculated/found) $C_{25}H_{27}N_3OS$

C : 72.36/72.27, H: 6.77/6.99, N: 9.74/9.46

mp : 179.4-181.0℃

IR (KBr) : 1664 cm^{-1}

NMR ($CDCl_3$) : 1.04 (3H, d, J=7.1 Hz), 1.53 (3H, d, J=6.6 Hz), 1.0-2.1 (10H, m), 2.07-2.5 (4H, m), 4.6-4.8 (1H, m), 7.26 (1H, d, J=8.1 Hz), 7.62 (1H, s), 7.8-8.0 (3H, m), 8.10 (1H, m), 8.75 (2H, m)

Mass (APCI, m/z) : 432 (M+1)

Preparation 25-1

The following compound was obtained in a similar manner to that of Preparation 23-1.

1-phenylcyclopropanecarboxylic acid methyl ester

NMR ($CDCl_3$) : 1.10-1.22 (2H, m), 1.57-1.63 (2H, m), 3.62 (3H, s), 7.20-7.43 (5H, m)

Mass (APCI, m/z) : 177 (M+1)

Preparation 25-2

The following compound was obtained in a similar manner to that of Preparation 21-2.

1-phenylcyclopropylmethanol

IR (neat) : 3359 cm^{-1}

NMR ($CDCl_3$) : 0.80-0.93 (4H, m), 1.51 (1H, s), 3.67 (2H, s), 7.16-7.40 (5H, m)

Mass (APCI, m/z) : 131 ($M-H_2O$)

Preparation 25-3

The following compound was obtained in a similar manner to that of Preparation 21-3.

1-phenylcyclopropanecarbaldehyde

NMR ($CDCl_3$) : 1.25-1.44 (2H, m), 1.50-1.74 (2H, m), 7.25-7.42 (5H, m), 9.29 (1H, s)

Mass (APCI, m/z) : 129 ($M-H_2O$)

Preparation 25-4

The following compound was obtained in a similar manner to that of Preparation 21-4.

3-(1-phenylcyclopropyl)acrylic acid ethyl ester

NMR ($CDCl_3$) : 1.23 (3H, t, J=7.1 Hz), 1.1-1.35 (4H, m), 4.12 (2H, q, J=7.1 Hz), 5.28 (1H, d, J=15.4 Hz), 6.69 (1H, d, J=15.4 Hz), 7.20-7.41

(5H, m)

Mass (APCI, m/z) : 217 (M+1)

Preparation 25-5

The following compound was obtained in a similar manner to that of Preparation 21-5.

3-(1-phenylcyclopropyl)propionic acid ethyl ester

IR (neat) : 1735 cm^{-1}

NMR ($CDCl_3$) : 0.66-0.85 (4H, m), 1.21 (3H, t, J=7.1 Hz), 1.6-2.4 (4H, m), 4.00-4.18 (2H, m), 7.10-7.33 (5H, m)

Mass (ESI, m/z) : 219 (M+1)

Preparation 25-6

The following compound was obtained in a similar manner to that of Preparation 21-6.

3-(1-phenylcyclopropyl)propionic acid

IR (KBr) : 1700 cm^{-1}

NMR ($CDCl_3$) : 0.65-8.86 (4H, m), 1.5-2.4 (4H, m), 7.07-7.33 (5H, m)

Mass (ESI, m/z) : 191 (M+Na)

Preparation 25-7

The following compound was obtained in a similar manner to that of Preparation 21-7.

4-ethyl-α-tetralone

IR (neat) : 1683 cm^{-1}

NMR ($CDCl_3$) : 1.02 (3H, t, J=7.4 Hz), 1.6-1.85 (2H, m), 2.00-2.4

(2H, m), 2.50-2.90 (3H, m), 7.25-7.37 (2H, m), 7.44-7.55 (1H, m), 8.00-8.05 (1H, dd, J=7 Hz and 2Hz)

Mass (ESI, m/z) : 175 (M+1)

Preparation 25-8

The following compound was obtained in a similar manner to that of Preparation 12.

1-hydroxyimino-4-ethyl-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3205 cm^{-1}

NMR ($CDCl_3$) : 0.96 (3H, t, J=7.3 Hz), 1.5-1.7 (2H, m), 1.8-2.0 (2H, m), 2.6-3.0 (3H, m), 7.14-7.35 (3H, m), 7.83-7.88 (1H, m), 9.28 (1H,br)

Mass (APCI, m/z) : 190 (M+1)

Preparation 25-9

The following compound was obtained in a similar manner to that of Preparation 12-(1).

5-ethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (KBr) : 1668 cm^{-1}

NMR ($CDCl_3$) : 0.97 (3H, t, J=7.3 Hz), 1.6-2.0 (3H, m), 2.2-2.6 (3H, m), 2.8-3.0 (1H, m), 6.95-7.08 (1H, m), 7.14-7.30 (3H, m), 8.17 (1H, br)

Mass (APCI, m/z) : 190 (M+1)

Preparation 25-10

The following compound was obtained in a similar manner to that of Preparation 1.

5-ethyl-7-chloroacetyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$) : 0.99 (3H, t, J=7.3 Hz), 1.7-2.0 (3H, m), 2.2-2.7 (3H, m), 2.7-3.0 (1H, m), 4.70 (2H, s), 7.16 (1H, d, J=8.2 Hz), 7.80-7.95 (1H, m), 8.13 (1H, d, J=2 Hz), 9.57 (1H, br)

Mass (APCI, m/z) : 266 (M+1)

Example 115

The following compound was obtained in a similar manner to that of Example 1.

5-ethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (KBr) : 1670 cm^{-1}

NMR ($CDCl_3$) : 1.03 (3H, t, J=7.3 Hz), 1.7-2.1 (3H, m), 2.3-2.7 (3H, m), 2.8-3.05 (1H, m), 7.09 (1H, d, J=8.1 Hz), 7.60 (1H, s), 7.83 (1H, dd, J=2 Hz and 8.1 Hz), 7.91 (2H, dd, J=4.5 Hz and 1.6 Hz), 8.14 (1H, d, J=2 Hz), 8.05 (1H, s), 8.75 (2H, dd, J=4.5 Hz and 1.6 Hz)

Mass (ESI, m/z) : 350 (M+1)

Example 116

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-5-ethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Analysis : (calculated/found) $C_{25}H_{27}N_3OS$

C : 70.56/70.37, H : 6.44/6.49, N : 10.73/10.50

mp : 103.6-105.0°C

IR (KBr) : 1656 cm^{-1}

NMR ($CDCl_3$) : 1.06 (3H, d, J=7 Hz), 1.49 (3H, d, J=6.8 Hz), 1.0-

1.6 (4H, m), 1.6-2.35 (4H, m), 2.35-2.60 (1H, m), 2.7-2.9 (1H, m), 4.85 (1H, pent, J=6.9 Hz), 7.31 (1H, d, J=8.8 Hz), 7.63 (1H, s), 7.8-7.9 (2H, m), 7.91 (2H, dd, J=4.6 Hz and 1.6 Hz), 8.75 (2H, dd, J=4.6 Hz and 1.6 Hz)

Mass (APCI, m/z) : 392 (M+1)

Preparation 26-1

The following compound was obtained in a similar manner to that of Preparation 21-1.

2-methyl-2-(4-methylphenyl)propionic acid methyl ester

NMR ($CDCl_3$) : 1.56 (6H, s), 2.32 (3H, s), 3.64 (3H, s), 7.0-7.3 (4H, m)

Mass (APCI, m/z) : 193 (M+1)

Preparation 26-2

The following compound was obtained in a similar manner to that of Preparation 21-2.

2-methyl-2-(4-methylphenyl)propanol

IR (neat) : 3380 cm^{-1}

NMR ($CDCl_3$) : 1.31 (6H, s), 2.32 (3H, s), 3.58 (2H, d, J=6.3 Hz), 7.10-7.30 (4H, m)

Mass (APCI, m/z) : 147 ($M-H_2O$)

Preparation 26-3

The following compound was obtained in a similar manner to that of Preparation 21-3.

2-methyl-2-(4-methylphenyl)propanal

NMR ($CDCl_3$) : 1.44 (6H, s), 2.34 (3H, s), 7.10-7.40 (4H, m), 9.47

(1H, s)

Preparation 26-4

The following compound was obtained in a similar manner to that of Preparation 21-4.

4-methyl-4-(4-methylphenyl)-2-pentenoic acid ethyl ester

NMR ($CDCl_3$) : 1.23 (3H, t, J=7.1 Hz), 1.44 (6H, s), 2.32 (3H, s) 4.18 (2H, q, J=7.1 Hz), 5.79 (1H, d, J=15.8 Hz), 7.11 (1H, d, J=15.8 Hz), 7.05-7.3 (4H, m)

Mass (APCI, m/z) : 233 (M+1)

Preparation 26-5

The following compound was obtained in a similar manner to that of Preparation 21-5.

4-methyl-4-(4-methylphenyl)pentanoic acid ethyl ester

IR (neat) : 1735 cm^{-1}

NMR ($CDCl_3$) : 1.20 (3H, t, J=7.1 Hz), 1.30 (6H, s), 1.8-2.1 (4H, m), 2.31 (3H, s), 4.04 (2H, q, J=7.1 Hz), 7.05-7.30 (4H, m)

Mass (ESI, m/z) : 233 (M-1)

Preparation 26-6

The following compound was obtained in a similar manner to that of Preparation 21-6.

4-methyl-4-(4-methylphenyl)pentanoic acid

IR (KBr) : 1710 cm^{-1}

NMR ($CDCl_3$) : 1.30 (6H, s), 1.85-2.20 (4H, m), 2.30 (3H, s) 7.05-7.30 (4H, m)

Mass (ESI, m/z) : 229 (M+Na)

Preparation 26-7

The following compound was obtained in a similar manner to that of Preparation 21-7.

4,4,7-Trimethyl-α-tetralone

IR (neat) : 1685 cm^{-1}

NMR ($CDCl_3$) : 1.37 (6H, s), 2.00 (2H, t, J=6.5 Hz), 2.35 (3H, s), 2.71 (2H, t, J=6.5 Hz), 7.25-7.40 (2H, m), 7.82 (1H, m)

Mass (ESI, m/z) : 211 (M+1)

Preparation 26-8

The following compound was obtained in a similar manner to that of Preparation 12.

1-hydroxyimino-4,4,7-trimethyl-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3293 cm^{-1}

NMR ($CDCl_3$) : 1.28 (6H, s), 1.74 (2H, t, J=6.9 Hz) 2.32 (3H, m), 2.88 (2H, t, J=6.9 Hz), 7.10-7.20 (1H, m), 7.21-7.30 (1H, m), 7.68 (1H, br)

Mass (APCI, m/z) : 204 (M+1)

Preparation 26-9

The following compound was obtained in a similar manner to that of Preparation 12-(1).

5,5,8-trimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (KBr) : 1677 cm^{-1}

NMR ($CDCl_3$) : 1.39 (6H, s), 2.00-2.15 (2H, m), 2.31 (3H, s),

2.30-2.45 (2H, m), 6.75 (1H, m), 6.90-7.00 (1H, m), 7.28 (1H, d, J=7.9 Hz), 8.28 (1H, br)

Mass (ESI, m/z) : 204 (M+1)

Preparation 26-10

The following compound was obtained in a similar manner to that of Preparation 1.

7-chloroacetyl-5,5,8-trimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (KBr) : 1691, 1668 cm^{-1}

NMR ($CDCl_3$) : 1.44 (6H, s), 2.00-2.20 (2H, m), 2.40-2.55 (2H, m), 2.51 (3H, s), 4.64 (2H, s), 6.90 (1H, s), 7.74 (1H,s), 8.95 (1H, br)

Example 117

The following compound was obtained in a similar manner to that of Example 1.

5,5,8-trimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

IR (KBr) : 1675 cm^{-1}

NMR ($CDCl_3$) : 1.44 (6H, s), 2.1-2.2 (2H, m), 2.35-2.55 (5H, m), 6.91 (1H, s), 7.41 (1H, s), 7.74 (1H, s), 7.90 (2H, dd, J=4.5 Hz and 2 Hz), 8.41 (1H, br), 8.73 (2H, dd, J=4.5 Hz and 2 Hz)

Mass (ESI, m/z) : 364 (M+1)

Example 118

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-5,5,8-trimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Anal : (calculated/found) $C_{25}H_{27}N_3OS \cdot 1.2HCl$

C : 67.64/67.87, H : 6.72/6.46, N : 9.86/9.90

mp : 185.7-186.6℃

IR (KBr) : 1660 cm^{-1}

NMR ($CDCl_3$) : 1.06 (3H, d, J=7.1 Hz), 1.53 (3H, d, J=6.6 Hz), 1.8-2.4 (4H, m), 2.51 (3H, s), 4.6-4.8 (1H, m), 7.11 (1H, s), 7.44 (1H, s), 7.63 (1H, s), 7.88 (2H, dd, J=4.5 Hz and 1.6 Hz), 8.74 (2H, dd, J=4.5 Hz and 1.6 Hz)

Mass (APCI, m/z) : 406 (M+1)

Example 119

The following compound was obtained similarly with using methyl iodide instead of isopropyl iodide to Example 6-(1).

1,5,5-trimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 126.7-130.2℃

IR (KBr) : 1654 cm^{-1}

NMR ($CDCl_3$) : 1.43 (6H, s), 2.11 (2H, t, J=7 Hz), 2.35 (2H, t, J=7 Hz), 3.35 (3H, s), 7.27 (1H, d, J=8 Hz), 7.61 (1H, s) 7.88 (1H, dd, J=2 Hz and 8 Hz), 7.91 (2H, dd, J=4.5 Hz and 1.6 Hz), 8.04 (1H, d, J=2 Hz), 8.75 (2H, dd, J=4.5 Hz and 1.6 Hz)

Mass (ESI, m/z) : 364 (M+1)

Example 120

The following compound was obtained similarly with using ethyl iodide instead of isopropyl iodide to Example 6-(1).

1-ethyl-5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Analysis: (calculated/found) $C_{22}H_{23}N_3OS \cdot 0.2H_2O$

C : 69.34/69.38, H : 6.19/6.15, N : 11.03/10.76

mp : 125.7-126.1℃

IR (KBr) : 1662 cm^{-1}

NMR ($CDCl_3$) : 1.34 (3H, t, J=7.1 Hz), 1.44 (6H, s), 2.0-2.2 (2H, m), 2.25-2.4 (2H, m), 3.87 (2H, q, J=7.1 Hz), 7.33 (1H, d, J=8.3 Hz), 7.62 (1H, s), 7.83-8.0 (1H, m), 7.91 (2H, d, J=5.8 Hz), 8.04 (1H, d, J=1.8 Hz), 8.74 (2H, d, J=5.8 Hz)

Mass (ESI, m/z) : 378 (M+1)

Example 121

The following compound was obtained similarly with using n-propyl iodide instead of isopropyl iodide to Example 6-(1).

1-propyl-5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Analysis : (calculated/found) $C_{23}H_{25}N_3OS \cdot 0.4H_2O$

C : 69.28/69.13, H : 6.52/6.38, N : 10.54/10.22

mp : 118.1-120.7℃

IR (KBr) : 1658 cm^{-1}

NMR ($CDCl_3$) : 0.97 (3H, t, J=7.4 Hz), 1.44 (6H, s), 1.7-1.95 (2H, m), 2.0-2.2 (2H, m), 2.25-2.4 (2H, m), 3.6-3.8 (2H, m), 7.33 (1H, d, J=8.3 Hz), 7.61 (1H,s), 7.83-8.0 (1H, m), 7.91 (2H, dd, J=4.5 Hz and 1.6 Hz), 8.04 (1H, d, J=2 Hz), 8.74 (2H, dd, J=4.6 Hz and 1.5 Hz)

Mass (ESI, m/z) : 392 (M+1)

Example 122

The following compound was obtained similarly with using n-

butyl iodide instead of isopropyl iodide to Example 6-(1).

1-butyl-5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Analysis : (calculated/found) $C_{23}H_{25}N_3OS \cdot 0.4H_2O$

C : 71.08/70.79, H : 6.71/6.78, N : 10.36/10.12

mp : 117.2-119.3℃

IR (KBr) : 1658 cm^{-1}

NMR ($CDCl_3$) : 0.96 (3H, t, J=7.2 Hz), 1.44 (6H, s), 1.25-1.5 (2H, m), 1.65-1.85 (2H, m), 2.0-2.2 (2H, m), 2.25-2.4 (2H, m), 3.65-3.8 (2H, m), 7.33 (1H, d, J=8.3 Hz), 7.61 (1H,s), 7.83-8.0 (1H, m), 7.91 (2H, dd, J=4.5 Hz and 1.6 Hz), 8.04 (1H, d, J=2 Hz), 8.74 (2H, dd, J=4.5 Hz and 1.6 Hz)

Mass (ESI, m/z) : 406 (M+1)

Example 123

The following compound was obtained similarly with using n-amyl iodide instead of isopropyl iodide to Example 6-(1).

1-pentyl-5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Analysis : (calculated/found) $C_{25}H_{27}N_3OS \cdot 0.2H_2O$

C : 70.79/71.11, H : 7.00/7.03, N : 9.93/9.84

mp : 134.0-136.1℃

IR (KBr) : 1644 cm^{-1}

NMR ($CDCl_3$) : 0.91 (3H, t, J=6.5 Hz), 1.44 (6H, s), 1.25-1.5 (4H, m), 1.65-1.85 (2H, m), 2.0-2.2 (2H, m), 2.25-2.4 (2H, m), 3.65-3.8 (2H, m), 7.33 (1H, d, J=8.3 Hz), 7.61 (1H, s), 7.83-8.0 (1H, m), 7.91 (2H, dd, J=4.6 Hz and 1.6 Hz), 8.05 (1H, d, J=2 Hz), 8.75 (2H, dd, J=4.6 Hz and 1.6 Hz)

Mass (ESI, m/z) : 420 (M+1)

Example 124

The following compound was obtained similarly with using n-hexyl iodide instead of isopropyl iodide to Example 6-(1).

1-hexyl-5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Analysis : (calculated/found) $C_{26}H_{31}N_3OS \cdot 0.3H_2O$

C : 71.13/71.12, H : 7.25/7.23, N : 9.57/9.53

mp : 107.9-110.1℃

IR (KBr) : 1646 cm^{-1}

NMR ($CDCl_3$) : 0.89 (3H, t, J=6.7 Hz), 1.44 (6H, s), 1.25-1.5 (6H, m), 1.65-1.85 (2H, m), 2.0-2.2 (2H, m), 2.25-2.4 (2H, m), 3.65-3.8 (2H, m), 7.33 (1H, d, J=8.3 Hz), 7.61 (1H, s), 7.83-8.0 (1H, m), 7.91 (2H, dd, J=4.5 Hz and 1.6 Hz), 8.05 (1H, d, J=2 Hz), 8.75 (2H, dd, J=4.5 Hz and 1.6 Hz)

Mass (ESI, m/z) : 434 (M+1)

Example 125

The following compound was obtained in a similar manner to that of Example 82.

5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepine-2-thione

NMR (d_6-DMSO) : 1.40 (6H, s), 2.0-2.25 (2H, m), 1.6-1.75 (2H, m), 7.20 (1H, d, J=8.3 Hz), 7.80-8.0 (1H, m), 7.98 (2H, dd, J=4.5-Hz and 1.6 Hz), 8.10 (1H, d, J=2 Hz), 8.40 (1H, s), 8.76 (2H, dd, J=4.5 Hz and 1.6 Hz)

Mass (APCI, m/z) : 367 (M+1)

Preparation 27-2

To a solution of 3-methyl-2-butenanilide (12.0 g, 68.5 mmol) in methylene chloride (180 ml) at room temperature was added aluminum chloride (6.0 g, 44.5 mmol). The whole mixture was heated with stirring for 6 hours, poured onto ice, and then extracted with methylene chloride. The organic layer was separated, and washed with water. The solvent was removed in vacuo to give 4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one as a white powder.

NMR ($CDCl_3$) : 1.34 (6H, s), 2.50 (2H, s), 6.8-7.35 (4H, m), 9.29 (1H, br)

Mass (ESI, m/z) : 176 (M+1)

Preparation 27-3

The following compound was obtained in a similar manner to that of Preparation 1.

6-chloroacetyl-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one

IR (KBr) : 1702, 1683 cm^{-1}

NMR ($CDCl_3$) : 1.39 (6H, m), 2.56 (2H, s), 4.66 (2H, s), 6.97 (1H, d, J=8.3 Hz), 7.80 (1H, dd, J=8.3 Hz and 1.9 Hz), 7.97 (1H, d, J=1.9 Hz), 9.70 (1H, s)

Mass (APCI, m/z) : 252 (M+1)

Example 129

The following compound was obtained in a similar manner to that of Example 1.

4,4-dimethyl-6-[2-(4-pyridyl)thiazol-4-yl]-3,4-dihydro-1H-quinolin-2-one

IR (KBr) : 1685 cm^{-1}

NMR ($CDCl_3$) : 1.43 (6H, s), 2.56 (2H, s), 6.96 (1H, d, J=8.2 Hz), 7.55 (1H, s), 7.78 (1H, dd, J=8.2 Hz and 1.8 Hz), 7.91 (2H, dd, J=4.6 Hz and 1.6 Hz), 7.96 (1H, d, J=1.7 Hz), 8.74 (2H, dd, J=4.6 Hz and 1.6 Hz)

Mass (ESI, m/z) : 336 (M+1)

Example 130

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-4,4-dimethyl-6-[2-(4-pyridyl)thiazol-4-yl]-3,4-dihydro-1H-quinolin-2-one

mp : 127.1-130.2℃

IR (KBr) : 1667 cm^{-1}

NMR ($CDCl_3$) : 1.38 (6H, s), 1.56 (6H, d, J=7.0 Hz), 4.7-4.9 (1H, m), 7.22 (1H, d, J=8.5 Hz), 7.56 (1H, s), 7.82 (1H, dd, J=8.5 Hz and 2 Hz), 7.85-8.0 (2H, m), 8.70-8.80 (2H, m)

Mass (APCI, m/z) : 378 (M+1)

Example 131

The following compound was obtained in a similar manner to that of Example 1-(1).

1-isopropyl-4,4-dimethyl-6-[2-(4-pyridyl)thiazol-4-yl]-1,2,3,4-tetrahydroquinoline dihydrochloride

mp : 127-131℃

IR (KBr) : 3419, 2607, 2497, 1631, 1511, 1469 cm^{-1}

NMR (DMSO-d_6, δ) : 1.19 (6H, d, J=6 Hz), 1.31 (6H, s), 1.70 (2H, t, J=6 Hz), 3.22 (2H, t, J=6 Hz), 4.1-4.3 (1H, m), 6.86 (1H, d, J=9 Hz), 7.7-8.0 (2H, m), 8.34 (1H, s), 8.51 (2H, d, J=7 Hz), 8.97 (2H, d, J=7 Hz)

Mass (m/z) : 364 $(M+1)^+$

Example 132

The following compound was obtained in a similar manner to that of Example 6-(1).

1'-methyl-7'-[2-(4-pyridyl)thiazol-4-yl]spiro[cyclohexane-1,5'-(1,3,4,5-tetrahydro-2H-1-benzazepin-2-one)]

mp : 142-145℃

IR (KBr) : 1653, 1597, 1477 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-2.4 (14H, m), 3.33 (3H, s), 7.26 (1H, d, J=8 Hz), 7.61 (1H, s), 7.8-8.1 (4H, m), 8.75 (2H, d, J=6 Hz)

Mass (m/z) : 404 $(M+1)^+$

Example 133

The following compound was obtained in a similar manner to that of Example 43.

4-[4-(1-isopropyl-5,5-dimethyl-1,3,4,5-tetrahydro-2-oxo-2H-1-benzazepin-7-yl)thiazol-2-yl]pyridine 1-oxide

mp : 227-229℃

IR (KBr) : 1658, 1475 cm^{-1}

NMR ($CDCl_3$, δ) : 1.03 (3H, d, J=7 Hz), 1.35 (3H, s), 1,5-1.6 (6H, m), 1.8-2.4 (4H, m), 4.6-4.9 (1H, m), 7.27 (1H, d, J=8 Hz), 7.63 (1H, s), 7.8-8.1 (4H, m), 8.31 (2H, d, J=7 Hz)

Mass (m/z) : 408 $(M+1)^+$

Preparation 28-1

The following compound was obtained in a similar manner to that of Preparation 12.

1-hydroxyimino-7-methoxy-1,2,3,4-tetrahydronaphthalene

NMR ($CDCl_3$, δ) : 1.7-2.0 (2H, m), 2.69 (2H, t, J=6 Hz), 2.80 (2H, t, J=7 Hz), 3.81 (3H, s), 6.8-7.1 (2H, m), 7.43 (1H, d, J=3 Hz), 8.97 (1H, s)

Mass (m/z) : 192 $(M+1)^+$

Preparation 28-2

The following compound was obtained in a similar manner to that of Preparation 12-(1).

8-methoxy-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 2.1-2.5 (4H, m), 2.73 (2H, t, J=7 Hz), 3.79 (3H, s), 6.5-6.8 (2H, m), 7.10 (1H, d, J=8 Hz), 8.33 (1H, s)

Mass (m/z) : 192 $(M+1)^+$

Preparation 28-3

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-8-methoxy-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

NMR ($CDCl_3$, δ) : 1.09 (3H, d, J=7 Hz), 1.45 (3H, d, J=7 Hz), 1.7-2.8 (6H, m), 3.82 (3H, s), 4.7-5.0 (1H, m), 6.7-6.8 (2H, m), 7.09 (1H, d, J=8 Hz)

Mass (m/z) : 234 $(M+1)^+$

Preparation 28-4

The following compound was obtained in a similar manner to that of Preparation 1.

1-isopropyl-7-chloroacetyl-8-hydroxy-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 126-129℃

IR (KBr) : 1645, 1618, 1495 cm^{-1}

NMR ($CDCl_3$, δ) : 1.0-1.5 (6H, m), 1.8-2.4 (4H, m), 2.5-2.8 (2H, m), 4.69 (2H, s), 4.6-4.9 (1H, m), 6.88 (1H, s), 7.50 (1H, s), 11.71 (1H, s)

Mass (m/z) : 296 $(M+1)^+$

Example 134

The following compound was obtained in a similar manner to that of Example 1.

1-isopropyl-7-[2-(4-pyridyl)thiazol-4-yl]-8-hydroxy-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 255-259℃

IR (KBr) : 3163, 1651, 1604, 1493 cm^{-1}

NMR ($CDCl_3$, δ) : 1.15 (3H, d, J=6 Hz), 1.49 (3H, d, J=6 Hz), 1.8-2.4 (4H, m), 2.5-2.9 (2H, m), 4.7-5.0 (1H, m), 6.94 (1H, s), 7.46 (1H, s), 7.71 (1H, s), 7.82 (2H, d, J=6 Hz), 8.79 (2H, d, J=6 Hz), 11.42 (1H, s)

Mass (m/z) : 380 $(M+1)^+$

Example 135

The following compound was obtained in a similar manner to that of Example 6-(1).

1-isopropyl-7-[2-(4-pyridyl)thiazol-4-yl]-8-methoxy-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

mp : 192-193℃

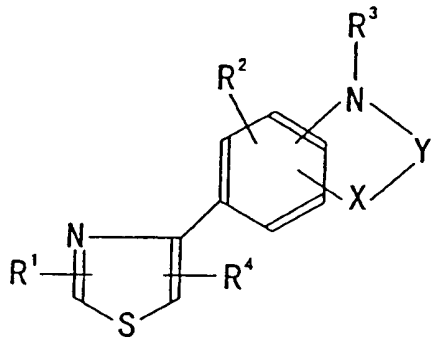
IR (KBr) : 1657, 1608 cm^{-1}

NMR ($CDCl_3$, δ) : 1.13 (3H, d, J=7 Hz), 1.50 (3H, d, J=7 Hz),

1.9-2.4 (4H, m), 2.7-2.9 (2H, m), 3.99 (3H, s), 4.8-5.0 (1H, m), 6.86 (1H, s), 7.92 (2H, d, J=6Hz), 8.09 (1H, s), 8.22 (1H, s), 8.73 (2H, d, J=6 Hz)

CLAIMS

1. A compound of the formula:



(I)

wherein

R^1 is amino;

lower alkylamino;

heterocyclic ring containing nitrogen which may be substituted with

halogen(s), amino(s), N-oxide, lower alkoxy(s), lower alkyl(s), lower alkoxycarbonyl(s), halo(lower)-alkoxycarbonyl(s), cyano(s), cyclo(lower)alkylamino(s), lower alkylamino(s), heterocyclic ring containing nitrogen(s), or oxo; or

lower alkyl substituted with heterocyclic ring containing nitrogen;

R^2 is hydrogen;

hydroxy;

lower alkyl; or

lower alkoxy;

R^3 is hydrogen;

lower alkyl which may be substituted with

acyl(s), N-mono(or di)(lower)alkylamino(s), lower

alkylthio(s), lower alkoxy(s), carboxy(s), heterocyclic ring containing nitrogen(s), lower alkynyl(s), halogen(s), or aryl(s);

acyl; or

cyclo(lower)alkyl;

R^2 and R^3 may be linked together to form lower alkylene,

R^4 is hydrogen;

lower alkyl;

halogen; or

lower alkylthio;

X is lower alkylene which may be substituted with

heterocyclic ring containing nitrogen(s), halogen(s), hydroxy(s), phenyl(lower)alkylidene(s), N-mono(or di)-(lower)alkylamino(lower)alkylidene(s), hydroxy(lower)alkylidene(s), or lower alkoxyimino(s);

cyclo(lower)alkylidene;

carbonyl; or

thio;

Y is lower alkylene which may be substituted with

oxo, or thioxo; and

X and Y may be linked together to form lower alkenylene,

X and N are respectively bonded to the adjoining carbon atoms on the benzene ring,

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1,

wherein

R^1 is amino;

lower alkylamino;

which is 1-isoproyl-8-methyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one.

7. A compound of claim 5,
which is 1-isoproyl-5,5-dimethyl-7-[2-(4-pyridyl)thiazol-4-yl]-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one.

8. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

9. A use of compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament for the prophylactic and/or therapeutic treatment of inflammatory conditions, autoimmune diseases, IFN-γ mediated diseases and TNF mediated diseases.

10. A method for treating or preventing inflammatory conditions, autoimmune diseases, IFN-γ mediated diseases and TNF mediated diseases which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

11. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 98/04275

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D417/04 C07D417/14 A61K31/425 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 03392 A (G.D SEARLE & CO.) 8 February 1996 see page 4 - page 6, line 28 ---	1,8
A	WO 94 29295 A (FUJISAWA PHARMACEUTICAL CO. LTD.) 22 December 1994 see page 1 - page 3 ---	1,8
A	WO 86 03749 A (RORER INTERNATIONAL INC.) 3 July 1986 see page 1 - page 7 ---	1,8
A	US 4 762 848 A (KARL-HEINZ SCHEUNEMANN ET AL.) 9 August 1988 see the whole document ---	1,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 1999	12/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kyriakakou, G

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 98/04275

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 4 725 606 A (DAVID A. BOULTON ET AL.) 16 February 1988 see the whole document	1,8
A	US 3 852 293 A (ZAVEN S. ARIYAN ET AL.) 3 December 1974 see the whole document	1,8

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Information on patent family members

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